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ABSTRACT
Derivatives of 2-spirocyclopropyl cephalosporin sulfoxide of the structural formula I

are provided which are useful as potent elastase inhibitors.

10 Claims, No Drawings
2-SPIROCYCLOPROPYL CEPHALOSPORIN SULFONE DERIVATIVES

This application is a continuation-in-part of application Ser. No. 07/418,075, filed Oct. 6, 1989.

The present invention relates to novel 2-spirocyclopropyl cephalosporin sulfone derivatives and to processes for their preparation.

BACKGROUND OF THE INVENTION

Emphysema is an abnormal and irreversible enlargement of the air spaces around the bronchioles caused by chronic inflammation. It is also characterized by the destruction of the alveolar walls of the lungs. As the damage to the alveolar walls increases the lungs lose their elasticity. The progressive symptoms include shortness of breath upon minimal exertion, frequent respiratory infections and chronic cough. Emphysema is considered to be one of the chronic pulmonary diseases.

The hydrolytic action of the enzyme human leukocyte elastase (HLE) on the connective tissue component elastin is believed to be the cause of pulmonary emphysema. Like other serine proteases, elastase may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Under normal conditions, these enzymes are prevented from causing damage by the action of the natural inhibitor α1-antitrypsin, which is a glycoprotein present in human serum.

It would appear that the inflammation caused by cigarette smoke provokes the release of a large amount of leukocyte elastase and hence an imbalance between the two enzymes results. The quantity of α1-antitrypsin present is thus insufficient to inhibit enough of the leukocyte elastase. Consequently the excess elastase begins adhering to the surfaces of elastin fibers in the lungs. This eventually leads to the lung damage characteristic of emphysema.

Additionally, it is believed that the action of cigarette smoke functions to inactivate the α1-antitrypsin. Also an α1-antitrypsin deficiency may be caused by hereditary factors.

Cephalosporin drugs are widely used for the treatment and prevention of various infectious diseases caused by pathogenic bacteria.


BRIEF SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided novel 2-spirocyclopropyl cephalosporin sulfones having anti-elastase activity. Such derivatives, or elastase inhibitors, are useful in the prevention, control and treatment of inflammatory conditions, particularly rheumatoid arthritis, osteoarthritis, cystic fibrosis and emphysema.

In one aspect, the present invention relates to a 2-spirocyclopropyl cephalosporin sulfone compound of formula I:

\[ R_1 \text{ is } OR_6; \text{ or NR}_7 R_8; \]
\[ R_2 \text{ is hydrogen; or a halogen; or a hydroxy group; or a } C_1-6 \text{ alk oxy group; or an optionally substituted } C_6-10 \text{ aryl group; or an optionally substituted } C_3-C_8 \text{ cycloalkyl group; or an optionally substituted aralkyl group; or an optionally substituted saturated or unsaturated monocyclic or fused polycyclic 3-8 membered heterocyclic group, or a halogenated } C_1-C_6 \text{ alkyl group, or a hydroxy } C_1-C_6 \text{ alkyl group, or a } C_7-C_10 \text{ alkanoyloxy } C_1-C_6 \text{ alkyl group, or a } -CH_2-CH(OH)-CH_2-C_3-C_6 \text{ alkyl group, or a } -CH_2-CH(OH)-C_3-C_6 \text{ alkyl group; or a COOH; or a } \text{C} \text{OOC}_2-C_3-C_6 \text{ alkyl group; or a } -CH_2-CH(OH)-C_3-C_6 \text{ alkyl group;}
\]

wherein

\[ R_1 \text{ is } OR_6; \text{ or NR}_7 R_8; \]
\[ R_2 \text{ is hydrogen; or a halogen; or a hydroxy group; or a } C_1-6 \text{ alk oxy group; or an optionally substituted } C_6-10 \text{ aryl group; or an optionally substituted } C_3-C_8 \text{ cycloalkyl group; or an optionally substituted aralkyl group; or an optionally substituted saturated or unsaturated monocyclic or fused polycyclic 3-8 membered heterocyclic group, or a halogenated } C_1-C_6 \text{ alkyl group, or a hydroxy } C_1-C_6 \text{ alkyl group, or a } C_7-C_10 \text{ alkanoyloxy } C_1-C_6 \text{ alkyl group, or a } -CH_2-CH(OH)-CH_2-C_3-C_6 \text{ alkyl group, or a } -CH_2-CH(OH)-C_3-C_6 \text{ alkyl group; or a COOH; or a } \text{C} \text{OOC}_2-C_3-C_6 \text{ alkyl group;}
\]

and treatment of inflammatory conditions, particularly rheumatoid arthritis, osteoarthritis, cystic fibrosis and emphysema.
group; or —COR; or an ary group; or an aralkyl group; or an optionally substituted heterocyclic group;
R10 is hydrogen, or R11—(CH2)n—C(O)—; or R11—X—(CH2)m—C(O)—; or R11SO2;
R11 is an optionally substituted C1—C6 alkyl group, or a trifluoromethyl group, or an optionally substituted phenyl group, or an optionally substituted heterocyclic group;
R12 is C1—C6 alkyl, C2—C6 alkenyl, C2—C6 alkynyl, phenyl, —CH2 phenyl; or a saturated or unsaturated, monocyclic or fused polycyclic 3—8 membered heterocyclic ring;
X is hydroxy; or halogen; or an acetate; C1—C6 alkoxy; or C2—C6 alkanoyloxy; or arylcarbonyloxy; or an amino group; or NH(C1—C6 alkyl); or a triazolyl group; or CONH2; or an N-alkyl derivative of CONH2; or an N,N-dialkyl derivative of CONH2; or

O
\[ \text{or } -\text{CONHC1—C6 alkyl or a quaternary ammonium group; } \]
Y is oxygen; or sulfur; or nitrogen;
\[ n \text{ is } 0 \text{ or } 1; \text{ and } m \text{ is } 1 \text{ or } 2. \]

In a second aspect, the present invention relates to a method for preparing 2-spirocyclopropyl cephalosporin sulfone derivatives which comprises the following steps:

(1) providing a compound having the general formula II:

(2) esterifying the compound of formula II to thereby protect the carboxy group thereof and provide a compound having the general formula III:

(3) halogenating the compound of formula III to provide a compound having the general formula IV:

(4) oxidizing the compound of formula IV to provide a compound having the general formula V;

(5) aminomethylating the compound of formula V to provide a compound having the general formula VI;

(6) carrying out a cycloaddition reaction to the compound of the general formula VI to provide a compound having the general formula I.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

As summarized above, the present invention relates to a 2-spirocyclopropyl cephalosporin sulfone derivative of the structural formula (I) is provided.
containing 3 to 7 carbon atoms, which may in addition also contain at least one hetero atom such as N, S, and O.

Representative examples of such groups are:

- \(-\text{N} -\text{N} -\text{COOH}\)
- \(-\text{N} -\text{CONHCH}_2\text{COOH}\)
- \(-\text{N} -\text{CONHCH}_2\text{COOH}\) (d- and l-form)
- \(-\text{N} -\text{CONHCH}_2\text{COOH}\) (d- and l-form)

or the like. These rings can be further substituted at the carbon or at the nitrogen atom by the groups mentioned above. Furthermore, the moiety NR_2R_8 may represent an amino acid, a dipeptide or a tripeptide moiety.

Preferably R_6 and R_7 are substituted or unsubstituted straight or branched loweralkyl, straight or branched loweralkenyl, cycloalkyl, haloalkyl, aryl, aralkyl, alkoxyloweralkyl, alkanoyloweralkyl, alkanoyloxyloweralkyl; and R_8 is the same as R_6 or hydrogen.

Preferred examples of such groups are methyl, ethyl, t-butyl, allyl, methoxyethyl, benzhydryl, benzyl, p-nitrobenzyl, p-methoxybenzyl, 2,2,2-trichloroethyl, pyrrolidine carboxamide, piperidine carboxamide, and the like.

R_2 is hydrogen, chloro, hydroxy, C_1-6 alkyl, C_1-6 alkenyl, C_1-6 alkynyl, cycloalkyl, C_1-6 alkoxy, trifluoromethyl, aldehyde, carboxylic acid; or \(-\text{CH}_2\text{X}\) wherein X is hydroxy, chloro, fluoro, C_1-6 alkoxy, C_2-6 alkanoyloxy; arylcarboxyloxy; amino; \(-\text{NHC}_1-6\text{alkyl};\) or a quaternary ammonium group (for example NH_3, NHZ_2, NZ_3 where Z represents lower alkyl, aryl or aralkyl); \(-\text{CONH}_2;\) \(-\text{CONH(C}_1-6\text{alkyl})_2;\) \(-\text{OCONH}_2\) or \(-\text{OCONH(C}_1-6\text{alkyl})_2\).

When \(\text{CH}_2\text{X}\) is hydroxymethyl, the cephalosporin can also exist as the lactone which is formed by internal esterification with the adjacent carboxyl group.

In the formula \(\text{CH}_2\text{X}\) when X is amino, the cephalosporin compound can also exist in the lactam form by loss of water with the adjacent carboxyl group.

R_2 can also be represented by the formula \(-\text{CH}_2\text{YR}_9\) where Y is oxygen; sulfur; or nitrogen. R_9 is an acyl group, a straight or branched loweralkyl; alkenyl; alkynyl; aryl; aralkyl; or a heterocyclic group such as heteroaryl, heterocycloalkyl. These groups can be substituted by one or more functional groups, such as alkyl, alkoxy, halo, cyano, carboxy, haloalkyl, amino, substituted amino, hydroxy, carboxyalkyl, carbamoylalkyl, sulfanyl, sulfonyl or the like.

In the formula \(-\text{CH}_2\text{YR}_9\) when Y is nitrogen, R_9 may represent the residue of amine. The term “the residue of an amine” for R_9 includes aliphatic, aromatic and heterocyclic primary amino residues. Suitable aliphatic amino primary residues include, for example, C_1-6 alkyl and C_1-6 cycloalkyl. Suitable primary aromatic amino residues include, for example, aryl and C_1-6 alkyl. Suitable secondary aliphatic amino residues include, for example, di C_1-6 alkyl. Suitable secondary aromatic amino residues include for example, diaryl and bis aryl C_1-6 alkyl. In the formula \(-\text{CH}_2\text{YR}_9\), Y may also be nitrogen which is part of the heterocyclic system, for example, morpholinio, 4-methyl (or ethyl) piperazino, pyrrrolidino, piperidino, pyridinium, etc.

Some representative examples of such groups are aminomethyl, N,N-dimethylaminomethyl, N,N-dimethylaminomethyl, 1,2,3-triazol-1-yl-methyl, 1,2,4-triazol-1-yl-methyl, triazoles substituted with one or more functional groups consisting of chloro, fluoro, bromo, hydroxy, carboxy, carbamethoxy, carboethoxy, hydroxyalkyl, cyano, amino, substituted amino, and the like.

Some representative examples of quaternary ammonium groups are:
In the formula $-\text{CH}_2\text{YR}_9$ when $Y$ is sulfur, $R_9$ may be hydrogen or the residue of a thiol compound. The term "residue of a thiol compound" means a residue obtained by omitting the $-\text{SH}$ group from a thiol compound. Suitable thiol compounds include a cyclic or acyclic aliphatic thiol, aromatic thiol, or a heteroaromatic thiol compound. Suitable aliphatic residues include: straight or branched chain alkyl having from 1 to 20 carbon atoms, especially methyl, ethyl, isopropyl, $t$-butyl, pentyl, hexyl, etc.; cycloalkyl having from 3 to 8 carbon atoms, especially cyclopentyl, cyclobutyl, cyclohexyl, etc.; alkenyl having from 2 to 20 carbon atoms especially $C_2$-$C_6$ alkynyl, such as vinyl, allyl, etc.; and alkynyl having from 2 to 20 carbon atoms, especially $C_2$-$C_6$ alkylnyl, such as ethynyl, propynyl or hexynyl, etc.

Suitable aromatic residues include: aryl having from 6 to 10 carbon atoms, especially phenyl. Phenyl can be substituted, for example, tolyl, aralkyl, for example, benzyl. Suitable heterocyclic groups include monoheteroaryls, di- or polynuclear, or fused heteroaryls containing from 1 to 3 of any one or more of the heteroatoms N, S, or O, in each heteroaryl ring.

Examples of such heterocyclic groups that might be mentioned are: unsaturated 3 to 8-membered heterocyclic systems containing 4 nitrogen atoms, for example, pyrrolidinyl, imidazolidinyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc) and tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc) saturated 3 to 8-membered heterocyclic groups containing 1 to 4 nitrogen atoms may include, for example, pyrrolidinyl, imidazolidinyl, piperidino, or piperazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms may comprise, for example, indolyl, quinolyl, benzimidazolyl, or benzotriazolyl; saturated 3 to 8-membered heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms may comprise, for example, morpholinyl; unsaturated 3 to 8-membered heterocyclic groups containing an oxygen atom would be furyl, for example; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms may include, for example, benzoazolyl, benzoazaindolyl; or unsaturated 3 to 8-membered heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, could comprise thia-
The substituents $R_3$ and $R_4$ in formula (I) may be the same or different and may comprise hydrogen; straight or branched loweralkenyl; straight or branched loweralkyl; cycloalkyl; haloalkyl; hydroxyalkyl; alkoxyloweralkyl; alkyloxyloweralkyl; aryl; aralkyl; -COOH; -CH₂COOH; -COOC₁₋₆ alkyl; -CH₃COOC₁₋₆ alkyl; trifluoromethyl; unsubstituted or substituted phenylthio C₁₋₆ alkyl; phenylsulfonyl C₁₋₆ alkyl; a monocyclic (or fused polycyclic) saturated or unsaturated heterocyclic group containing from 1 to 3 of any one or more of the heteroatoms N, S or O in each heterocyclic ring; heteroaryalkyl such as 2-pyridylmethyl, 2-thienylmethyl or the like.

The above groups can be further substituted with one or more groups such as alkyl, alkoxy, hydroxy, halogen, haloalkyl, hydroxyalkyl, nitro, amino, substituted amino, cyano, carbonyl, acyloxy, carboxamide, sulfinyl, sulfonyl, etc.

More preferably $R_3$ and $R_4$ are hydrogen; C₁₋₆ alkyl, especially methyl, ethyl, isopropyl, t-butyl, n-pentyl; halo C₁₋₆ alkyl, especially chloromethyl, fluoromethyl; cyclopropyl, phenyl, p-chlorophenyl, p-fluorophenyl, benzyl, p-carboxmethoxybenzyl, p-carboxmethoxyphe- nyl, trifluoromethyl, -COOH, CH₂COOH, CH₂COOC₁₋₆ alkyl especially CH₂COOCH₃, CH₂COOEt, pyridyl, thienyl, furyl, isoxazolyl, and the like.

The substituent $R_5$ in formula (I) can be hydrogen, or a halogen (e.g., chloro, bromo or fluoro), or a hydroxy group or C₁₋₆ alkoxy especially methoxy, ethoxy, propoxy; C₁₋₄ alkylthio especially methylthio, ethylthio; a lower alkylsulfanyl group such as methylsulfanyl, ethylsulfanyl; a lower alkane sulfonyl group such as methane sulfonylethane sulfonylethoxy; an acyloxy group. The "acyl group" can be a lower alkanyl group of 2 to 6 carbon atoms such as COCH₃, COC₂H₅ or COC₆H₄+.

Further examples of "acyl" groups include haloloweralkanoyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl. Suitable examples of acyloxy may also include, for example, methane sulfonfyoxy, trifluoromethane sulfonfyoxy, benzene-sulfonfyoxy, tolune sulfonfyoxy or the like.

The substituent $R_9$ can be represented by the formula:

$$R_9 = \text{NH}$$

where $R_{10}$ represents a substituted or unsubstituted aliphatic, aromatic or heterocyclic, aliphatic or heterocyclylaliphatic carboxylic acid radical known in the penicillin and cephalosporin art.

In the formula R₁₀NH, R₁₀ may represent hydrogen; or

$$R_{10} = \begin{cases} \text{NH} & \text{if } n = 0, 1, 2 \\ \text{S-C₆H₅-alkyl, -S-phenyl} & \text{if } n \geq 3 \end{cases}$$

which may be substituted or unsubstituted and $n$ is an integer of 0 to 2, preferably 2. Representative members of sulfonamido group are: phenylsulfonamide, trifluoromethane sulfonamide, methyl sulfonamide, ethyl sulfonamide, and the like.

The carboxylic acid radicals can be represented by the general formula

$$R_{11} = \text{CH}_3 \text{COO}$$

wherein $n$ is 0, 1 or 2 and $R_{11}$ is:

(a) straight or branched chain alkyl having from 1 to 20 carbon atoms, especially methyl, ethyl, trifluoro-

(b) aryl having from 6 to 10 carbon atoms, especially phenyl, substituted phenyl;

(c) monoheterocaroyl, di- or polyheteroaryl, or fused heteroaryl containing from 1 to 3 of any one or more of the heteroatoms N, S or O in each heterocyclic ring such as thienyl, furyl, pyridyl, iso-thiazolyl, imidazolyl, isoxazolyl and the like; or

(d) hydrogen.

The above groups can be substituted with one or more functional groups such as alkyl, alkoxy, halo such as fluoro, chloro, bromo, iodo, cyano, carbonyl, carboxyl, sulfonyl, amino, substituted amino such as monoalkylamino, dialkylamino, haloalkyl, carboxyl, carboxamoyl, carboxamoylalkyl, and guanidino.

Representative examples of such acyl groups include: methyl, ethyl, cyanomethyl, trifluoromethyl, dichloro-

(benzyl, p-hydroxybenzyl, 2-furylmethyl, and 2-thiophenylmethy.

The carboxylic acid radical can also be represented by the general formula:

$$R_{11} = X = \text{CH}_3 \text{COO}$$

wherein $X$ is 0 or S and $R_{11}$ and $n$ are as previously defined.

Representative examples of such acyl groups include: phenoxyacetyl, phenylthiobenzy, phenoxyethyl, 4-

Preferably $R_3$ is hydrogen, chloro, bromo, fluoro, hydroxy, methoxy, ethoxy, methylsulfonamide, ethyl-

Further examples of acyl groups include halolower-

where $R_{11}$ is hydrogen, methyl, trifluoromethyl, cyano-

$$R_{11} = \text{CH}_3 \text{COO}$$

and n is 0 or 1; or
R11—X—(CH2)n—CO wherein X is oxygen or sulfur and R11 and n are as defined before.

More preferably, R5 is hydrogen, chloro, bromo, fluoro, methoxy, ethoxy, methylsulfonyl, trifluoromethyl sulfonamide, methanesulfonyl, trifluoromethane sulfonamide and m is 0, 1 or 2, preferably 2.

The partial structure represented by the formula:

\[
\begin{align*}
\text{(O)_m} & \quad \text{COR} \\
& \quad R_3 \\
& \quad R_4 \\
& \quad R_2 \\
& \quad R_1
\end{align*}
\]

is to be understood to include both the region isomers as represented by the formula:

Furthermore, it should be noted that when R3 and R4 in formula (I) are different they may be present in the form of an optical isomer, for example, l-, d- or dl-forms.

More specifically the most preferred embodiments of the present invention comprise the following compounds:

- Benzhydryl 7α-chloro-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- Benzhydryl 7α-bromo-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- Benzhydryl 7β-7,7-dihydro-2-spiro 2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- t-Butyl 7α-bromo-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- Benzhydryl 7α-bromo-2-spiro [2',2',4',4'-dichloro)diphenyl] cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- Benzhydryl 7α-bromo-2-spiro [2',2',4',4'-difluoro)diphenyl] cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
- t-Butyl 7α-chloro-2-spiro (2',2'-diphenyl) cyclopropyl-3-acetoxymethyl-3-cephem-4-carboxylate-1,1-dioxide;
- Benzhydryl 7α-bromo-2-spiro (2'-ethoxycarbonyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;

In accordance with a second broad aspect of the invention, there is provided a process for preparing 2-spirocyclol propyl cephalosporin sulfone derivatives of the structural formula I which comprises the following steps (Scheme I).

1. Providing a compound having the structural formula II;
2. Esterifying the compound of formula II to thereby protect the carboxy group thereof and provide a compound having the structural formula III;
(3) halogenating the compound of formula III to provide a compound having the structural formula IV;

(4) oxidizing the compound of formula IV to provide a compound having the structural formula V;

(5) aminoethylating the compound of formula V to provide a compound having the structural formula VI;

(6) carrying out a cycloaddition reaction of the compound of the structural formula VI to provide a compound having the structural formula I.

Alternatively steps (2) and (3) may be conducted in reverse order.

The following synthetic routes are useful in preparing the compound having the structural formula (I):

There is also provided a method for preparing 7-substituted cephalosporin derivatives which comprises the following steps: (Scheme II)

(1) providing the compound having the formula VII;

(2) treating the compound VII with an appropriate alcohol (e.g., methanol, ethanol, etc.) to provide a compound having the formula VIII;

(3) oxidizing the compound VIII with a suitable oxidizing agent (e.g., m-chloro peroxy benzoic acid, per-
acetic acid, etc.) to provide a sulfoxide having the formula IX;

(4) heating the compound IX with a suitable mercaptan (e.g., 2-mercaptobenzothiazole) in a suitable organic solvent (e.g., benzene, toluene, etc.) to provide the compound having the formula X

(5) treating the compound X with a suitable halogenating agent (e.g., chlorine, bromine, etc.) to provide a compound having the formula XI

(6) treating the compound XI with an organic base (e.g., pyridine, triethylamine, etc.) in a solvent like dimethyl sulfoxide to provide the 7-substituted cephalosporin derivative having the formula XII

Alternatively, cephalosporin derivative XII can also be obtained by heating the sulfoxide IX with acetic anhydride in dimethyl formamide.

The following synthetic routes are useful in preparing the 7-substituted cephalosporin derivative XII (Scheme II)

Esterification or Amidation

The carboxyl group of compound II can be protected according to the conventional methods described in the cephalosporin and penicillin literature. For example, a suitable salt of the compound II may be reacted with an alkyl halide, such as, benzyl bromide, 4-nitrobenzyl bromide, methyl iodide, allyl bromide or the like. The salts of compound II may be salts with an inorganic base such as alkali metal salts (e.g., sodium or potassium) or an alkaline earth metal salt (e.g., calcium or magnesium), the hydroxide, carbonate or bicarbonate thereof, a salt with an organic base such as trimethylamine, triethylamine, pyridine, N,N-dialkylamine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]-octane, 1, 8-diazabicyclo[5, 4, 0]undec-7-ene etc.
The carboxyl group of compound II can also be converted into an ester by other alkylation methods, for example, by treatment with diazomethane or diphenyl-diazomethane or the like.

The carboxyl group can be converted to an ester by treatment with a lower alkanol e.g., methanol, ethanol, in the presence of a catalyst such as hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, tri-chloroacetic acid, trifluoroacetic acid, or toluenesulfonic acid and a Lewis acid. Suitable Lewis acids for this reaction include, for example, boron halide (e.g., boron trichloride, boron trifluoride, titanium halide (e.g., titanium chloride, titanium bromide), stannic halide, aluminum halide, zinc chloride, ferric chloride and the like.

Treatment with a lower alkene (e.g., isobutylene), in the presence of a suitable acid catalyst (e.g., sulfuric acid) is also a preferable method of protecting the carboxyl group.

Esterification can also be carried out in the presence of a conventional condensing agent such as N,N-dicyclohexylcarbodiimide, N,N-diethylcarbodiimide, N,N-diisopropylcarbodiimide, or N,N-carbonyldimidazole.

Another method of esterification (also suitable for amidation) is by conversion of the carboxyl group to a suitable reactive derivative followed by reaction with an appropriate alcohol (or amine). Suitable reactive derivatives of the carboxyl group may include an acid halide, a mixed or symmetrical anhydride, an activated amide or the like. A suitable example may be an acid chloride or bromide via treatment with a halogenating agent such as thionyl chloride, phosphorus pentachloride or phosphorus oxychloride.

The reactions are usually carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

An interesting class of amides is that where the amine reactant is an amine acid or a peptide. The amino acid may be one of the naturally occurring amino acids, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamic acid, aspartic acid, lysine, arginine, phenylalanine, tyrosine, proline, hydroxyproline and tryptophan, or peptides containing or made from these amino acids. Of particular interest are amides made from amines which are dipeptides, such as proline-alanine, proline-valine, and proline-glycine.

The procedure used to prepare amides wherein the amine reactant is an amino acid or peptide is essentially the same as that used for the preparation of peptides. Such procedures are well known to those skilled in the art and involve the selective protection of end groups, a coupling step to form the peptide or amide bond, and a deprotection step. For example, dipeptides are prepared by activation of the carboxyl group in an N-protected amino acid (using Z or Boc as the blocking group) and adding an amino acid ester to the activated carboxyl group (the C-protecting group is an alkyl or benzyl ester). Tri- and higher peptides are prepared in a similar manner. It is noted that the carboxylic acid corresponding to the compound of formula I (R=OH) may optionally contain an amino group, which, if present, would be protected as is customary in peptide synthesis.

Halogenation

It should be noted that when it is appropriate the compound II can be halogenated first and then subjected to esterification according to the procedures as described above.

The compound IV, wherein R₃ is a halogen, can be prepared by subjecting the amino group of compound II to the diazotization reaction in accordance with conventional methods in the presence of a hydrogen halide or a metal halide. Suitable hydrogen halides used in the present reaction include, for example, hydrogen chloride, hydrogen bromide, and hydrogen iodide. Suitable metal halides include sodium bromide, potassium bromide, and cupric chloride. The present reaction is preferably carried out under mild conditions such as under cooling, at ambient or slightly elevated temperatures.

Oxidation

The compound V in the present invention can be prepared by oxidizing the compound IV. The present oxidizing reaction is carried out under conditions wherein the —S— group can be converted to the sulfone or sulfone, most preferably to the sulfone. Typical oxidizing agents can be utilized such as for example, phenylisodichloride, ozone, isocyanuoryl chloride, periodic acid, perbenzoic acid, m-chloroperbenzoic acid, performic acid, peracetic acid, trifluoroperacetic acid, or hydrogen peroxide.

The present oxidizing reaction is usually carried out in the presence of a solvent such as chloroform, methylene chloride, dioxane, benzene, ethyl acetate, or other solvents which does not adversely affect the reaction. The reaction is usually carried out at room temperature or under cooling.

Aminomethylation (Mannich Reaction)

The introduction of the exocyclic double bond at the 2-position of compound V can be carried out according to the procedure detailed in the literature; [I. G. Wright et al., J. Med. Chem., 14, 420 (1971), incorporated herein by reference]. The reaction is usually carried out in a solvent such as alcohol (e.g. t-butanol), methylene chloride, chloroform, carbon tetrachloride, mixed solvent thereof, or any other solvent not adversely affecting the reaction.

There is no particular limitation to the reaction temperature and the present reaction is usually carried out from room temperature to about 150°C. with or without reflux until the reaction is complete.

Cycloaddition

For the introduction of the 2-spirocyclopropyl groups which may be substituted with suitable substituents, the reaction is carried out by reacting the compound VI with a compound of the formula R₃R₄CN₂ where R₃ and R₄ may be the same or different and represent the groups as defined earlier herein. The reaction is usually carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, benzene, ether, ethyl acetate or any other solvent which does not adversely affect the reaction. The reaction is usually carried out under cooling to ambient temperature.

Biological Evidence

The in vitro test data on anti-elastase activity of exemplary derivatives having the structural formula I are shown in Table I herebelow.
<table>
<thead>
<tr>
<th>R3</th>
<th>m</th>
<th>R3</th>
<th>IC50 (µg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>2</td>
<td>OCH₃Ph₂</td>
<td>0.022</td>
</tr>
<tr>
<td>Br</td>
<td>2</td>
<td>OCH₃Ph₂</td>
<td>0.0032</td>
</tr>
<tr>
<td>H</td>
<td>2</td>
<td>OCH₃Ph₂</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Br</td>
<td>2</td>
<td>CH₂Cl</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

The compounds tested were as follows:

- Benzhydryl-7α-chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
- Benzhydryl-7α-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
- Benzhydryl-7,7-dihydro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
- t-Butyl 7α-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
- Benzhydryl-7α-bromo-2-spiro(2',2'-dichloro)-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
- Benzhydryl-7α-bromo-2-spiro(2',2'-dichloro)-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.

Benzhydryl-7α-chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-acet oxymethyl-3-cephem-4-carboxylate-1, 1-dioxide.

Benzhydryl-7α-bromo-2-spiro(2'-ethoxycarbonyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.

Benzhydryl-7α-bromo-2-spiro(2'-phenyl-2'-methyl)cyclopropyl -3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.

Benzhydryl-7α-bromo-2-spiro(2'-phenyl)-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.

Benzhydryl-7α-bromo-2-spiro(2'-phenyl)-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.

7α-Bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-pyrrolidine carboxamide-1, 1-dioxide.

7α-methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-pyrrolidine carboxamide-1, 1-dioxide.

2,2,2-Trichloroethyl-7α-ethoxy-2-spiro(2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide.
**Benzhydryl-7α-methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide.**

5,264,430

The enzyme activity was determined by monitoring the increase in absorbance at 405 nm caused by the hydrolysis of chromogenic substrates. Inhibition of enzyme by the compounds described were determined after a 10 minute preincubation with the enzyme in reaction mixture minus substrate. Reaction was initiated by the addition of substrate. The concentration of human leukocyte elastase used for assay was at 10 nM.

In order to demonstrate the specificity of the compounds of formula I against human leukocyte elastase, some of these compounds were further tested against various proteases and the IC50 values are shown in Table II herebelow.

### Table II

**SELECTIVITY OF 1-SPIROCYCLOPROPYL CEPHALOSPORIN SULFONES AGAINST VARIOUS PROTEASES IC50 (μg mL⁻¹)**

| R₁ | R₂ | R₃ (or R₄) | R₄ (or R₅) | TRY | THR | PLM | CTC | APN | CTG | CTD | PPE |
|----|----|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Br | OCH₂Ph | Ph | Ph | 26.2 | 26.2 | 2.1 | 26.2 | 26.2 | 10.6 | 32.7 | 0.012 |
| Cl | OCH₂Ph | Ph | Ph | 36.6 | 24.4 | 2.2 | 36.6 | 26.6 | 12.2 | 10.5 | 0.020 |
| Br | OBu | Ph | Ph | 21.8 | 21.8 | 3.0 | 21.8 | 21.8 | 21.8 | 27.2 | 0.051 |
| Br | OCH₂Ph | H | COOH | 0.333 | 23 | 6.32 | 23 | 23 | 7.47 | 27.7 | 0.018 |
| Br | OCH₂Ph | p-Cl-Cl₂H₄ | p-Cl-Cl₂H₄ | 40 | 40 | 1.6 | 40 | 40 | 14.0 | 33.4 | 0.17 |
| Br | OCH₂Ph | p-F-Cl₂H₄ | p-F-Cl₂H₄ | 27.6 | 27.6 | 2.2 | 27.6 | 27.6 | 13.1 | 34.5 | 0.044 |
| Br | OCH₂Ph | CH₃ | CH₃ | 0.089 | 23.7 | 3.26 | 23.7 | 23.7 | 23.7 | 29.6 | 0.033 |
| Br | Ph | Ph | 21.1 | 21.1 | 21.1 | 5.29 | 5.29 | 21.1 | 5.29 | 0.11 |

| E:O | OCH₂CCl₃ | Ph | Ph | 5.85 | 5.85 | 5.85 | 5.85 | 5.85 | 0.187 | 5.85 | 0.0094 |
| CH₃O | OCH₂Ph | Ph | Ph | 6.06 | 6.06 | 5.33 | 6.06 | 6.06 | 6.06 | 6.06 | 0.035 |
| CH₃O | OCH₂CCl₃ | Ph | Ph | 0.37 | 5.70 | 0.742 | 5.70 | 5.70 | 0.23 | 5.70 | 0.013 |
| CH₃O | Ph | Ph | 5.07 | 20.2 | 5.07 | 5.07 | 5.07 | 5.07 | 5.07 | 0.016 |

**PROTOCOL**

**Enzyme Assay for Inhibition of HLE**

**Enzyme:** Purified elastase from human white blood cells

**Substrate:** MeO-succinyl-L-alanyl-L-alanyl-L-propyl-L-valine-p-nitroanilide (NA)

**Reaction Mixture:**
- 10 mM phosphate buffer (pH 7.6)
- 500 mM NaCl

**PROTOCOL**

**Porcine Pancreatic Elastase (PPE)**

**Enzyme:** Purified elastase from porcine pancreas

**Substrate:** MeO-succinyl-L-alanyl-L-alanyl-L-prolyl-L-valine-pNA

**Reaction mixture:**
- 50 mM Tris[Tris(hydroxymethyl) aminomethane],
- HCl buffer (pH 8.9)
- 500 mM NaCl
Cathepsin G (CTG)

Enzyme: Purified Cathepsin G from human white blood cells
Substrate: N-succinyl-L-alanyl-L-alanyl-L-phenylalanyl-L-phenylalanine-p-NA
Reaction mixture:
10 mM Phosphate buffer (pH 7.5)  
500 mM NaCl  
10% DMSO  
2.0 mM Substrate

Trypsin (TRY)

Enzyme: Purified trypsin from bovine pancreas
Substrate: Bz-L-arginine-p-NA
Reaction mixture:
50 mM Tricine-NaOH buffer (pH 8.8)  
150 mM NaCl  
10% DMSO  
1.0 mM Substrate

Thrombin (THR)

Enzyme: Purified thrombin from human plasma
Substrate: Tosylglycyl-L-prolyl-L-arginine-p-NA acetate
Reaction mixture:
50 mM Tricine-NaOH buffer (pH 8.6)  
500 mM NaCl  
0.1% Polyethylene glycol 8000  
10% DMSO  
0.5 mM Substrate

Plasmin (PLM)

Enzyme: Purified plasmin from human plasma
Substrate: Tosylglycyl-L-prolyl-L-lysine-pNA acetate
Reaction mixture:
50 mM Tris-HCl buffer (pH 8.9)  
500 mM NaCl  
5% DMSO  
0.5 mM Substrate

Cathepsin C (CTC)

Enzyme: Purified cathepsin C from bovine spleen
Substrate: Glycyl-L-phenylalanine-pNA
Reaction mixture:
50 mM Citrate buffer (pH 5.4)  
5 mM B-Mercaptoethanol  
150 mM NaCl  
10% DMSO  
20 mM Substrate

Aminopeptidase M (APM)

Enzyme: Purified aminopeptidase M from porcine kidney
Substrate: L-Leucine-pNA
Reaction mixture:
50 mM Tricine buffer (pH 7.5)  
500 mM NaCl  
10% DMSO  
2.0 mM Substrate

Cathepsin D (CTD)

Enzyme: Purified cathepsin D from bovine spleen
Substrate: Hemoglobin (bovine)
Reaction mixture:

250 mM Glycine buffer (pH 3.2)  
10% DMSO

Except for Cathepsin D, the enzyme activities were determined by monitoring the increase in absorbance at 410 nm caused by the hydrolysis of chromogenic substrates. The activity of Cathepsin D was determined by monitoring the absorbance of 5% trichloracetic acid-soluble material at 280 nm.

Inhibition of enzymes by the compounds described were determined after a 10 minute preincubation with enzymes in reaction mixtures minus substrate. Reactions were initiated by the addition of substrates. The concentration used for assays were porcine pancreatic elastase at 240 nM and human Cathepsin G at 50 nM. Cathepsin D was used at the concentration that produced approximately 0.15 O.D. increase per 20 min at 280 nm under the standard conditions. All other proteases were assayed at the concentrations that produced approximately 0.1 O.D. change per minute at 410 nm under the standard conditions.

The compounds which had an IC50 value of less than 0.104M for HLE were tested against serine proteases (pancreatic elastase, leukocyte cathepsin G, trypsin, thrombin and plasmin), a cysteine protease (cathepsin C), metalloprotease (aminopeptidase M) and an aspartyl protease (cathepsin D). The results clearly demonstrate the highly selective nature of the inhibition of human leukocyte elastase by these compounds. The specificity of the compounds indicate that they should have little side effects caused by non-specific inhibition of proteases other than HLE when used in the treatment of various ailments in which HLE is the major causative agent.

For therapeutic administration, a compound having the structural formula I is used in the form of conventional pharmaceutical preparation which contains said compounds as an active ingredient in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparations may be in solid form such as capsule, tablet, ointment, etc. or in liquid form such as solution, suspension or emulsion. There may be included in the above preparation auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and the other commonly used additives.

In general, a daily dose of between 0.2 mg and 150 mg or even more per kilogram of body weight per day may be administered to a patient. However, the dose level may vary and will depend upon a variety of factors such as the activity of the specific compound employed, the age, body weight, sex, diet, time of administration, route of administration, etc.

The following examples are provided to demonstrate the operability of the present invention. The structures of the compounds were established by the modes of synthesis, by infrared spectroscopy, and by extensive high field nuclear magnetic resonance spectral techniques and x-ray analysis.
EXAMPLE 1

Benzhydryl 7a-chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

**STEP A: Preparation of 7a-chloro-3-methyl-3-cephem-4-carboxylic acid**

A mixture of 7-ADCA (25 g, 0.117 mol), ethanol (700 ml), water (163 ml) and concentrated hydrochloric acid (163 ml) was cooled to 5°C. Sodium nitrite (11.5 g, 0.167 mol) was added in small portions over 25 minutes and the mixture was stirred for 3.5 hours at 0-5°C; 300 ml of brine was added and the reaction mixture was extracted with methylene chloride. The organic extract was washed with water, brine, dried over sodium sulfate and concentrated (16.1 g, 58.9%). This crude acid was directly used for the next step without further purification.

**STEP B: Preparation of benzydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate**

The 7a-chloro-3-methyl-3-cephem-4-carboxylic acid (10.0 g, 0.0428 mol) was dissolved in methylene chloride (200 ml) and diphenylidiazomethane (10.8 g, 0.0557 mol) dissolved in methylene chloride (50 ml) was added dropwise over 30 minutes. The mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure and the product was purified over silica column using hexane-ethyl acetate mixture to yield benzhydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate (7.8 g, 45.6%).

NMR (CDCl3) δ 2.1 (s, 3H, CH3), 3.25 (bs, 2H, H-2), 4.70 (bs, 1H), 4.75 (bs, 1H), 7.0 (s, 1H, CHPh2), 7.3-7.7 (m, 10H, aromatic).

**STEP C: Preparation of benzydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide**

Benzhydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate (7.6 g, 0.019 mol) was dissolved in methylene chloride (50 ml) and peracetic acid (13.0 g, 0.171 mol) was added dropwise over 15-20 minutes with ice-cooling. The mixture was stirred for 72 hours at room temperature and was then washed successively with portions of water, saturated sodium bicarbonate solution, and water. Drying over sodium sulfate, filtration, removal of the solvent under reduced pressure and filtration of the residue through a small column of silica gel using methylene chloride as eluant gave 9.3 g of benzhydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide as a white foam.

NMR (CDCl3) δ 2.1 (s, 3H, CH3), 3.8 (bs, 2H, H-2), 4.75 (bs, 1H), 5.3 (bs, 1H), 7.0 (s, 1H, CHPh2), 7.4 (bs, 10H, aromatic).

**STEP D: Preparation of benzydryl 7a-chloro-2-methylen-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide**

Benzhydryl 7a-chloro-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide (9.3 g, 0.0215 mol) was dissolved in methylene chloride (35 ml), dimethylamine hydrochloride (4.9 g, 0.0645 mol), formaldehyde solution (2.25 g, 0.075 mol) and 2-butyralcohol (300 ml) were added and the mixture was heated to reflux at 95°C for 4 hours. After removing the solvent under reduced pressure the residue was redissolved in methylene chloride, washed successively with water, dried over sodium sulfate and concentrated. The product was purified over a silica column using hexane-ethyl acetate mixture as the eluant to yield benzhydryl 7a-chloro-2-methylen-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide (3.6 g, 40%) as a white foam. IR (Nujol) v max 1723, 1800 cm⁻¹.

NMR (CDCl3) δ 2.01 (s, 3H, CH3), 4.82 (d, 1H, J = 1.5 Hz), 5.3 (d, 1H, J = 1.5 Hz), 6.12 (d, 1H, exomethylene, J = 2.0 Hz), 6.22 (d, 1H, exomethylene, J = 2.0 Hz), 6.93 (s, 1H, CHPh2), 7.25-7.39 (m, 10H, aromatic).

**EXAMPLE 2**

STEP A: Preparation of 7a-bromo-3-methyl-3-cephem-4-carboxylic acid

To an ice-cooled mixture of 7-ADCA (10.0 g, 0.4667 mol), ethanol (270 ml), water (83 ml) and hydrobromic acid (48%, 56.7 ml), sodium nitrite (4.67 g, 0.0769 mol) was added in small portions over 25 minutes and the mixture was stirred for 2.5 hours at ice-temperature. Ethanol was removed under reduced pressure and the residual mass was diluted with methylene chloride, washed with water. The aqueous washings were saturated with brine and re-extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to give 9.8 g (75.5%) of 7a-bromo-3-methyl-3-cephem-4-carboxylic acid. This crude acid was directly used for the next step without further purification.

STEP B: Preparation of benzydryl 7a-bromo-3-methyl-3-cephem-4-carboxylate

To a stirred solution of 7a-bromo-3-methyl-3-cephem-4-carboxylic acid (9.8 g, 0.0353 mol) in 50 ml of dry methylene chloride was added dropwise a solution of diphenylidiazomethane (8.21 g, 0.04228 mol) dissolved in 50 ml of methylene chloride. The mixture was stirred at room temperature for 3 hours, washed with sodium bicarbonate solution, water, brine and concentrated to give 11.91 g (76%) of the crude product as a brown foam.

The above crude product was purified over a silica column with a mixture of hexane-ethyl acetate (85:15) to give 8.02 g (51.2%) of pure benzydryl 7a-bromo-3-methyl-3-cephem-4-carboxylate.
STEP C: Preparation of benzhydryl
7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

Benzhydryl 7α-bromo-3-methyl-3-cephem-4-carboxylate (16.0 g, 0.036 mol) was dissolved in methylene chloride (75 ml), peracetic acid (24.6 g, 0.324 mol) was added slowly and the mixture was stirred for 72 hours at room temperature, the mixture was washed successively with water, sodium bicarbonate solution and water. Drying over sodium sulfate, filtration, removal of solvent under reduced pressure, and purification of the residue over a silica column using methylene chloride as eluant gave benzhydryl α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (6.7 g, 40%) as a pale yellow foam.

NMR (CDCl3) δ 2.1 (s, 3H, CH3), 3.8 (bs, 2H, H-2), 4.8 (bs, 1H), 5.25 (bs, 1H), 6.95 (s, 1H, CHPh2), 7.2-7.6 (m, 10H, aromatic).

STEP D: Preparation of benzhydryl
7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

To a stirred solution of benzhydryl 7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (2.8 g, 0.0059 mol) in methylene chloride (12 ml) were added dimethyamine hydrochloride (1.44 g, 0.0176 mol), formaldehyde (0.61 g, 0.020 mol) and t-butyl alcohol (100 ml), the mixture was heated to reflux at 95°C for 3 hours. Solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was purified by column chromatography with a solvent gradient of 10 to 25% ethyl acetate/hexane to afford benzhydryl 7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (2.0 g, 69.5%) as a white foam. IR (Nujol) v max 1720, 1800 cm⁻¹.

NMR (CDCl3) δ 2.10 (s, 3H, CH3), 4.93 (d, 1H, J = 1.5 Hz), 5.33 (d, 1H, J = 1.5 Hz), 6.20 (d, 1H, exomethyne, J = 2 Hz), 6.7 (d, 1H, exomethyne, J = 2 Hz), 6.50 (s, 1H, CHPh2), 7.30-7.45 (m, 10H, aromatic).

STEP E: Preparation of benzhydryl
t-butyl 7α-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

Benzhydryl 7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (0.6 g, 0.00123 mol) was dissolved in methylene chloride (50 ml) and cooled to −15°C, diphenyl diazomethane (0.263 g, 0.00135 mol) was added to the solution and the mixture was stirred at room temperature for 3 hours. Evaporation of the solvent under reduced pressure gave a light pink foam which was purified by column chromatography with a solvent gradient of 10 to 30% ethyl acetate/hexane to afford benzhydryl 7α-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide. IR (Nujol) v max 1728, 1790 cm⁻¹.

NMR (CDCl3) δ 1.03 (s, 3H, CH3), 2.38 (d, 1H, cyclopropyl, J = 7 Hz), 2.96 (d, 1H, cyclopropyl, J = 7 Hz), 5.04 (d, 1H, J = 1.8 Hz), 5.20 (d, 1H, J = 1.8 Hz), 7.0 (s, 1H, CHPh2), 7.22-7.47 (m, 20H, aromatic).

EXAMPLE 3

t-Butyl 7α-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

STEP A: Preparation of t-butyl
7α-amino-3-methyl-3-cephem-4-carboxylate

A mixture of 7-ADCA (10.0 g, 0.0467 mol), ethylene glycol dimethyl ether (80 ml), concentrated sulfuric acid (6.0 ml) and isobutylen (36.0 g, 0.6416 mol) in a pressure bottle was stirred at room temperature for 32 hours. Solvent was removed under reduced pressure. The residue was diluted with methylene chloride, washed with water, sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to give 4.18 g of t-butyl 7α-amino-3-methyl-3-cephem-4-carboxylate.

NMR (CDCl3) δ 1.55 (s, 9H, t-butyl), 2.07 (s, 3H), 2.25 (bs, 2H, exchanged with D2O), 3.12 (d, 1H, J = 18.0 Hz), 3.59 (d, 1H, J = 18.0 Hz), 4.70 (d, 1H, J = 4.0 Hz), 4.95 (d, 1H, J = 4.0 Hz).

STEP B: Preparation of t-butyl
7α-bromo-3-methyl-3-cephem-4-carboxylate

To an ice-cooled mixture of t-butyl 7α-amino-3-methyl-3-cephem-4-carboxylate (1.3 g, 0.0048 mol), ethanol (30 ml), water (8.5 ml), hydrobromic acid (48%, 5.83 ml), sodium nitrite (0.48 g, 0.00696 mol) was added portionwise over 15 minutes and the mixture was stirred at ice temperature (−5°C) for 3 hours, saturated with sodium chloride, extracted with ethyl acetate (3 times). The combined ethyl acetate extract was washed with water, brine, dried and concentrated to give 800 mg (50%) of pure t-butyl 7α-bromo-3-methyl-3-cephem-4-carboxylate.

NMR (CDCl3) δ 1.54 (s, 9H, t-butyl), 2.10 (s, 3H), 3.20 (d, 1H, J = 18.0 Hz), 3.60 (d, 1H, J = 18.0 Hz), 4.71 (d, 1H), 4.85 (d, 1H).

STEP C: Preparation of t-butyl
7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

To a solution of t-butyl 7α-bromo-3-methyl-3-cephem-4-carboxylate (800 mg, 2.39 mmol) in methylene chloride (3 ml) was added peracetic acid (32%, 5.12 ml) and the mixture was stirred at room temperature for 48 hours, diluted with methylene chloride, washed with water, brine, dried and concentrated to give 700 mg (80%) of t-butyl 7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide. This product was directly used for the next step.

NMR (CDCl3) δ 1.55 (s, 9H, t-butyl), 2.10 (s, 3H), 3.63 (d, 1H, J = 18.0 Hz), 3.98 (d, 1H, J = 18.0 Hz), 4.83 (d, 1H), 5.33 (d, 1H).

STEP D: Preparation of t-butyl
7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

A mixture of t-butyl 7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (700 mg, 1.9 mmol), dimethylamine hydrochloride (460 mg, 5.7 mmol), methylene chloride (3 ml) and t-butyl alcohol (50 ml), formaldehyde (0.57 g, 37% w/v) was heated to reflux at 80°-90°C for 20 hours. T-Butyl alcohol was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with water, brine, dried and concentrated to give 200 mg of crude product which
was purified over silica column using methylene chloride as eluant to give 40 mg of pure t-butyl 7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate, 1H-dioxide.

NMR (CDCl₃) δ 1.55 (s, 9H, t-butyl), 2.15 (s, 3H), 4.95 (d, 1H), 5.32 (d, 1H), 6.21 (d, 1H), 6.70 (d, 1H).

**STEP E: Preparation of t-butyl 7α-bromo-2-spiro(2,2’-diphenyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylate, 1H-dioxide**

To a solution of t-butyl 7α-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate, 1H-dioxide (40 mg) in 7 ml of methylene chloride was added diphenyldiazomethane (23 mg) and the mixture was stirred at ice-temperature for 3 hours, after removal of the solvent the crude product was purified by preparative tlc to give 30 mg of pure t-butyl 7α-bromo-2-spiro(2,2’-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate, 1H-dioxide.

NMR (CDCl₃) δ 1.10 (s, 3H, CH₃), 1.55 (s, 9H, t-butyl), 2.37 (d, 1H, J = 7 Hz), 2.96 (d, 1H, J = 7 Hz), 5.03 (d, 1H, J = 2 Hz), 5.18 (d, 1H, J = 2 Hz), 7.23-7.48 (m, 10H, aromatic).

**EXAMPLE 4**

7α-chloro-2-spiro(2,2’-diphenyl)cyclopropyl-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide

**STEP A: Preparation of t-butyl 7α-amino-3-acetoxyethyl-3-cephem-4-carboxylate**

Dry dioxane was freed from peroxide by passage through a column of neutral activated alumina. To 100 ml of this solvent was added, in turn, with ice-cooling 10 ml of concentrated H₂SO₄, 10.9 g of 7-ACA and 50 ml of liquid isobutylene. The mixture was sealed in a pressure bottle, stirred at 30°C for 2 hours, poured into excess of ice-cold aqueous sodium bicarbonate solution. The solution was extracted with ethyl acetate. The combined ethyl acetate extract was washed with brine and dried over sodium sulfate. Evaporation of the filtrate under reduced pressure gave a light brown foam, 8.3 g (63%) of t-butyl 7α-amino-3-acetoxyethyl-3-cephem-4-carboxylate.

NMR (CDCl₃) δ 1.56 (s, 9H, t-butyl), 1.8 (s, 2H, NH₂) 2.1 (s, 3H, COOCH₃), 3.45 (ABq, 2H, H-2, J = 18 Hz), 4.54-5.2 (m, 4H, H-6-7 + H-7 + H-2 + H-2 + COOCH₃).

**STEP B: Preparation of t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate**

To an ice-cooled solution of t-butyl 7α-amino-3-acetoxyethyl-3-cephem-4-carboxylate (4.0 g, 0.0122 mol) in 75 ml of ethanol, 16.7 ml of water and 16.7 ml of concentrated hydrochloric acid was added portionwise over 15-20 minutes sodium nitrite (1.18 g, 0.017 mol). The reaction mixture was stirred at 0°-5°C for 2.5 hours, saturated with sodium chloride, extracted with methylene chloride, washed with water, brine, dried Na₂SO₄ and concentrated to give 3.1 g (73%) of t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate.

NMR (CDCl₃) δ 1.56 (s, 9H, t-butyl), 2.1 (s, 3H, COOCH₃), 3.5 (ABq, 2H, H-2, J = 18 Hz), 4.6-5.1 (m, 4H, H-6-7 + H-7 + H-2 + COOCH₃).

**STEP C: Preparation of t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide**

To a solution of t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate (3.1 g) in 50 ml of methylene chloride was added peracetic acid (22 ml) dropwise and the mixture was stirred at room temperature overnight. The reaction mixture was washed with water, sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, concentrated and the crude product was purified over silica column using hexane-ethyl acetate (3:1) to give 1.9 g (48%) of pure t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide.

NMR (CDCl₃) δ 1.55 (s, 9H, t-butyl), 2.1 (s, 3H, COOCH₃), 3.9 (ABq, 2H, H-2, J = 18 Hz), 4.8 (bs, 1H), 4.95 (ABq, 2H, CH₂OOCCH₃, J = 14 Hz), 5.3 (bs, 1H).

**STEP D: Preparation of t-butyl 7α-chloro-2-methylene-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide**

A mixture of t-butyl 7α-chloro-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide (19 g), methylene chloride (3 ml), dimethylaminohydrochloride (0.817 g), t-butanol (80 ml) and formaldehyde solution (1.10 ml, 37% w/w in water) was heated to reflux at 90°C for 3 hours. Solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with water, brine, dried and concentrated to give 1.6 g (81.6%) of t-butyl 7α-chloro-2-methylene-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide, m.p. 148°-149°C. This product without further purification was used in the next step.

**STEP E: Preparation of t-butyl 7α-chloro-2-spiro(2,2’-diphenyl)cyclopropyl-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide**

To an ice-cooled solution of t-butyl 7α-chloro-2-methylene-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide (200 mg, 0.51 mmol) in 15 ml of methylene chloride was added a solution of diphenyl diazomethane (109 mg) in 5 ml of methylene chloride and the mixture was stirred at room temperature for 2 hours. After removal of the solvent the crude product was purified by preparative tlc to afford pure t-butyl 7α-chloro-2-spiro(2,2’-diphenyl)cyclopropyl-3-acetoxyethyl-3-cephem-4-carboxylate, 1H-dioxide (113 mg, 40%), m.p. 163°-165°C.

NMR (CDCl₃) δ 1.55 (s, 9H, t-butyl), 2.01 (s, 3H, COOCH₃), 2.37 (d, 1H, J = 7 Hz), 3.03 (d, 1H, J = 7 Hz), 5.12 and 4.08 (dd, 2H, CH₂OOCCH₃, J = 13 Hz), 5.01 (d, 1H, J = 2 Hz), 5.26 (d, 1H, J = 2 Hz), 7.22-7.46 (m, 10H, aromatic).

**EXAMPLE 5**

Benzhydryl 7,7-dihydro-2-spiro(2,2’-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate, 1H-dioxide

Following substantially the same procedure as described in Example 1, step E, 0.6 g of benzhydryl 7,7-dihydro-2-methylene-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide in 50 ml of methylene chloride was treated with diphenyldiazomethane to give 0.34 g (39.4%) of benzhydryl 7,7-dihydro-2-spiro(2,2’-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide. IR (Nujol) ν max 1735, 1786 cm⁻¹.

NMR (CDCl₃) δ 1.02 (s, 3H, CH₃), 2.34 (d, 1H, cyclopropyl, J = 7 Hz), 2.94 (d, 1H,cyclopropyl, J = 7 Hz), 3.48 (ABX, 2H, H-7, J = 2.5, 5.0, 16.0 Hz), 5.03 (dd, 1H, H-6, J = 2.5, 5.0 Hz), 7.0 (s, 1H, CHFPPh₂), 7.2-7.48 (m, 20H, aromatic).
EXAMPLE 6

7a

Bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-pyrrrolidine carboxamide, 1,1-dioxide

STEP A: Preparation of 7a-bromo-2-methylene-3-methyl-3-cephem-4-carboxylic acid, 1,1-dioxide

To an ice-cooled stirred solution of benzhydryl 7a-bromo-2-methylene-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide (from step D, Example 2, 1.0 g, 2.047 mmol) in dry anisole (10 ml) was added trifluoracetic acid (4.0 ml) and the mixture was stirred at ice-temperature for 1 hour; solvent was removed under reduced pressure to leave a yellow oil. Hexane was added directly to the yellow oil while a white solid was precipitated out which was collected by filtration (0.549 g, 83%).

NMR (CDCl$_3$ + DMSO-d$_6$) δ 2.19 (s, 3H, CH$_3$), 5.13 (d, 1H), 5.44 (d, 1H), 6.27 (d, 1H), 6.69 (d, 1H).

STEP B: Preparation of 7a-bromo-2-methylene-3-methyl-3-cephem-4-pyrrrolidine carboxamide, 1,1-dioxide

7a-Bromo-2-methylene-3-methyl-3-cephem-4-carboxylic acid, 1,1-dioxide (440 mg, 1.366 mmol) was dissolved in 5 ml of methylene chloride and cooled to $-20^\circ$ C; to this solution phosphorus oxychloride (0.133 ml, 1.434 mmol) was added over 10 minutes and the mixture was stirred at $-20^\circ$ C for 30 minutes. Pyrrolidine (0.456 ml, 5.464 mmol) was added and the mixture was stirred at $-20^\circ$ C for 2 hours. To the mixture, ice-water was added and stirred for 15 minutes, methylene chloride layer was separated out and the aqueous layer was reextracted with methylene chloride. The combined methylene chloride layer was washed with water, citric acid, brine, dried over anhydrous sodium sulfate and concentrated to give 400 mg (78%) of brown solid which was purified over silica column using ethyl acetate-acetonitrile (9:1) as eluent. Pure product (89 mg, 17.4%) was isolated as white solid.

NMR (CDCl$_3$) δ 1.92 (s, 3H, CH$_3$), 1.85-2.1 (m, 4H, pyrrolidine), 3.42-3.73 (m, 4H, pyrrolidine), 4.98 (d, 1H, J = 1.6 Hz), 5.37 (d, 1H, J = 1.6 Hz), 6.0 (d, 1H, J = 1.8 Hz), 6.54 (d, 1H, J = 1.8 Hz).

STEP C: Preparation of 7a-bromo-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-pyrrrolidine carboxamide, 1,1-dioxide

To an ice-cooled solution of 7a-bromo-2-methylene-3-methyl-3-cephem-4-pyrrrolidine carboxamide, 1,1-dioxide (60 mg, 0.1599 mmol) in 3 ml of methylene chloride was added diphenyl diazomethane (31 mg, 0.1599 mmol). The reaction mixture was stirred at ice-temperature for 1.5 hours and then concentrated to give 80 mg of the crude product which was purified by preparative tlc (30 mg, 35%).

NMR (CDCl$_3$) δ 0.93 (s, 3H, CH$_3$), 1.86-2.0 (m, 4H, pyrrolidine), 2.275 (d, 1H, J = 7.0 Hz, cyclopropyl), 2.94 (d, 1H, J = 7.0 Hz, cyclopropyl), 3.42-3.68 (m, 4H, pyrrolidine), 5.05 (d, 1H, J = 1.6 Hz), 5.20 (d, 1H, J = 1.6 Hz), 7.18-7.49 (m, 10H, aromatic).

EXAMPLE 7

2,2,2-Trichloroethyl-7a-ethoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide

STEP A: Preparation of 2,2,2-trichloroethyl-6a-ethoxy-2,2-dimethylpenicillanate

To an ice-cooled solution of 6a-diazopenicillanate (5.0 g, 0.01395 mol) in a mixture of ethanol (10 ml) and methylene chloride (20 ml) was added boron trifluoromethane (4 drops). The mixture was stirred at ice-temperature for 3 hours, washed with water, brine, dried and concentrated to give 4.56 g (87%) of crude product which was purified over silica column using hexane-ethyl acetate (4:1) as eluant. The yield of pure product was 3.4 g (54.1%).

NMR (CDCl$_3$) δ 1.25 (t, 3H), 1.55 (s, 3H), 1.6 (s, 3H), 3.75 (q, 2H), 4.65 (s, 2H), 4.8 (s, 2H), 5.30 (s, 1H).

STEP B: Preparation of 2,2,2-trichloroethyl-6a-ethoxy-2,2-dimethylpenicillanate 1-oxide

To an ice-cooled solution of 2,2,2-trichloroethyl-6a-ethoxy-2,2-dimethyl penicillanate (3.4 g, 9.026 mmol) in 40 ml of methylene chloride was added m-chloroperbenzoic acid (80%, 1.95 g, 9.026 mmol) portionwise over 30 minutes. The mixture was stirred at ice-temperature until tlc indicates that all starting material has been consumed. The reaction mixture was washed with sodium bicarbonate solution, water, brine, dried and concentrated to give 4.0 g of crude product which was purified over silica column using methylene chloride as eluent (3.0 g, 84%).

NMR (CDCl$_3$) δ 1.3 (t, 3H), 1.34 (s, 3H), 1.80 (s, 3H), 2.85 (q, 2H), 4.65 (s, 1H), 4.80 (s, 1H), 5.02 (s, 3H).

STEP C: Preparation of 2,2,2-trichloroethyl-7a-ethoxy-3-methyl-3-cephem-4-carboxylate

A solution of 2,2,2-trichloroethyl-6a-ethoxy-2,2-dimethylpenicillanate 1-oxide (1.0 g, 2.546 mmol) in a mixture of DMF (10 ml) and acetic anhydride (0.659 ml) was heated to reflux at 125°-130° C. for 1.5 hours. Solvent was removed under reduced pressure and the residual dark oil was diluted with methylene chloride and was washed successively with water, sodium bicarbonate solution, brine, dried and concentrated to give 910 mg of the crude product which was purified on a silica column using methylene chloride as eluant, yield (400 mg, 42%).

NMR (CDCl$_3$) δ 1.28 (t, 3H), 2.165 (s, 3H), 3.215 (d, 1H, J = 17.3 Hz), 3.51 (d, 1H, J = 17.3 Hz), 3.62-3.88 (m, 2H), 4.57 (d, 1H, J = 1.4 Hz), 4.72 (d, 1H, J = 1.4 Hz), 4.80 (d, 1H, J = 12 Hz), 5.06 (d, 1H, J = 12 Hz).

STEP D: Preparation of 2,2,2-trichloroethyl-7a-ethoxy-3-methyl-3-cephem-4-carboxylate, 1,1-dioxide

To an ice-cooled solution of 2,2,2-trichloroethyl-7a-ethoxy-3-methyl-3-cephem-4-carboxylate (340 mg, 0.9075 mmol) in methylene chloride (14 ml), perchloric acid (32%, 1.94 ml) was added dropwise and the mixture was stirred at room temperature for 24 hours. Iced water was added to the reaction mixture and the organic layer was separated out; the aqueous solution was saturated with solid sodium chloride and re-
extracted with methylene chloride. The combined organic layer was washed with sodium bicarbonate solution, water, brine, dried over anhydrous sodium sulfate and concentrated to give 370 mg of the crude product which was purified over silica column using hexane-ethyl acetate (4:1) mixture, yield (300 mg, 81%).

NMR (CDCl₃) δ 1.29 (t, 3H), 2.16 (s, 3H), 3.68 (d, 1H, J=18.0 Hz), 3.92 (d, 1H, J=18 Hz), 3.67-3.96 (m, 2H), 4.67 (bs, 1H), 4.83 (d, 1H, J=11.7 Hz), 5.035 (d, 1H, J=11.7 Hz), 5.22 (d, 1H, J=1.4 Hz).  

**STEP E: Preparation of 2,2,2-trichloroethyl-7a-ethoxy-2-methylene-3-methyl-3-cephec-4-carboxylate-1,1-dioxide**

2,2,2-Trichloroethyl 7a-ethoxy-3-methyl-3-cephec-4-carboxylate 1,1-dioxide (290 mg, 0.7131 mmol) was dissolved in methylene chloride (5 ml), dimethylanilinium hydrochloride (168 mg, 2.066 mmol), formamide, and solution (0.19 ml, 2.375 mmol, 37% w/v) and t-butyl alcohol (3.3 ml) was heated to reflux at 70-75°C for 1.5 hours; solvent was removed under reduced pressure, the residue was diluted with methylene chloride and washed with water, brine, dried and concentrated to give 300 mg of white solid which was directly used for the next step without further purification.

NMR (CDCl₃) δ 1.30 (t, 3H), 2.19 (s, 3H), 3.67-3.89 (m, 2H), 4.805 (d, 1H, J=11.8 Hz), 5.12 (d, 1H, J=11.8 Hz), 4.86 (d, 1H), 5.32 (d, 1H), 6.17 (d, 1H, J=2.0 Hz), 6.68 (d, 1H, J=2.0 Hz).

**STEP F: Preparation of 2,2,2-Trichloroethyl-7a-ethoxy-2-spiro (2',2'- diphenyl)cyclopropyl-3-methyl-3-cephec-4-carboxylate-1,1-dioxide**

To an ice-cooled solution of 2,2,2-trichloroethyl 7a-ethoxy-3-methyl-3-cephec-4-carboxylate 1,1-dioxide (100 mg, 0.2388 mmol) in methylene chloride (5 ml) was added diphenyldiazomethane (56 mg, 0.2866 mmol) and the mixture was stirred at ice-temperature for 2 hours; solvent was removed under reduced pressure and the crude product was purified over silica column using methylene chloride as eluant to give 68 mg of pure 2,2,2-trichloroethyl 7a-ethoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephec-4-carboxylate 1,1-dioxide. NMR (CDCl₃) δ 1.16 (s, 3H, CH₃), 1-22 (t, 3H), 2.38 (d, 1H, J=7.0 Hz), Cyclopropyl, 2.98 (d, 1H, J=7.0 Hz, cyclopropyl), 3.46-3.82 (m, 2H), 4.67 (d, 1H, J=11.7 Hz), 5.02 (d, 1H), 5.11 (d, 1H), 5.24 (d, 1H, J=11.7 Hz), 7.17-7.50 (m, 10H, aromatic).

**EXAMPLE 8**

2,2,2-Trichloroethyl 7a-ethoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephec-4-carboxylate 1,1-dioxide

**STEP A: Preparation of 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate**

To an ice-cooled solution of 6-diazopenicillanate (5.0 g, 0.01395 mol) in a mixture of methanol (25 ml) and methylene chloride (25 ml) was added boron trifluoroetherate (4-5 drops) and the mixture as stirred at ice-temperature for 2 hours, washed with water, brine dried and concentrated to give 3.4 g of crude product which was purified over silica column using hexane-ethyl acetate (3:2) as eluant to give 2.3 g of pure 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate.

NMR (CDCl₃) δ 1.55 (s, 3H), 1.61 (s, 3H), 3.55 (s, 3H, OCH₃), 4-625 (doublet overlapped with a singlet, 2H), 4-79 (d, 2H), 5-35 (d, 1H).

**STEP B: Preparation of 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate-1-oxide**

To an ice-cooled solution of 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate (35.6 g, 0.09816 mol) in methylene chloride (350 ml) was added dropwise peracetic acid (15-4 ml, 32%). The mixture was stirred at ice-temperature for one hour, washed with water, sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and concentrated to give 26.0 g of 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate-1-oxide.

NMR (CDCl₃) δ 1.34 (s, 3H), 1.75 (s, 3H), 3.58 (s, 3H, OCH₃), 4.60 (s, 1H), 4.96 (s, 2H), 4.63 (d, 1H, J=12.0 Hz), 5.03 (d, 1H, J=12.0 Hz).

**STEP C: Preparation of 2,2,2-trichloroethyl-2-(benzothiazol-2'-ylidithio)-α-isopropenyl-4-oxo-3a-methoxy azetidine-1-acetate**

A mixture of 2,2,2-trichloroethyl-6a-methoxy-2,2-dimethyl penicillanate-1-oxide (15.0 g, 0.0396 mol) and 2-mercaptobenzothiazole (7.44 g, 0.04357 mol) in 250 ml of dry toluene was heated to reflux for 2 hours using a Dean-Stark trap; solvent was removed under reduced pressure. The residual brown oil dissolved in methylene chloride and precipitated with hexane under ice-cooling. The precipitated solid (18.4 g, 86%) was collected by filtration and used for the next step.

**STEP D: Preparation of 2,2,2-trichloroethyl-6a-methoxy-2,2-bromomethyl-2-methyl penicillanate**

2,2,2-Trichloroethyl-2-(benzothiazol-2'-ylidithio)-α-isopropenyl-4-oxo-3a-methoxy azetidine-1-acetate (7.4 g, 0.01408 mol) was dissolved in methylene chloride (100 ml) and cooled to -30°C; bromine (0.431 ml, 0.0084 mol) dissolved in methylene chloride was added dropwise to the above solution and the mixture was stirred at -30°C for 40 minutes, the precipitated solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residual mass was redissolved in ether and cooled, the precipitated solid was filtered off. The filtrate was concentrated to give a foam (6.0 gm). This product was used in the next step.

NMR (CDCl₃) δ 1.67 (s, 3H), 3.55 (s, 5H, OCH₃+CH₂Br), 4.67 (s, 1H), 4.80 (s, 2H), 5.30 (s, 1H), 5.45 (s, 1H).

**STEP E: Preparation of 2,2,2-trichloroethyl-7a-methoxy-3-methyl-3-cephec-4-carboxylate**

The crude mass (6.0 gm) from Step D was dissolved in a mixture of dimethyl sulfoxide (100 ml) and pyridine (9.0 ml) and the reaction mixture was stirred at room temperature for 20 hours; solvent was removed under reduced pressure. The sticky mass was dissolved in methylene chloride, washed successively with water, dilute hydrochloric acid, brine, dried and concentrated to give a semi solid (5.0 g).

NMR (CDCl₃) δ 2.15 (s, 3H), 3.37 (d, 2H), 3.55 (s, 3H), 4.58 (s, 1H), 4.77 (s, 2H), 4.90 (s, 1H).
STEP F: Preparation of 2,2,2-trichloroethyl-7α-methoxy-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

2,2,2-Trichloroethyl-7α-methoxy-3-methyl-3-cephem-4-carboxylate (8.7 g, 24.12 mmol) was dissolved in 100 ml of methylene chloride, peracetic acid (51.6 ml) was added dropwise and the mixture was stirred at room temperature for 18 hours. After the reaction, the reaction mixture was washed with water, sodium bicarbonate solution, brine, and dried to give a sticky solid. To the sticky mass a mixture of ether: hexane (1:1) was added with ice-cooling. The precipitated solid was collected by filtration (9.33 g, 98.5%). NMR (CDCl3) δ 2.17 (s, 3H), 3.57 (s, 3H), 4.13 (d, 2H), 4.93 (s, 1H) 5.15 (d, 1H), 5.20 (s, 1H), 5.96 (d, 1H).

STEP G: Preparation of 2,2,2-trichloroethyl-7α-methoxy-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

A mixture of 2,2,2-trichloroethyl-7α-methoxy-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (2.0 g, 5.094 mmol), dimethylamine hydrochloride (1.24 g, 15.28 mmol), t-BuOH (24 ml), methylene chloride (5 ml) and formaldehyde (1.43 ml, 37% w/v in water) was heated to reflux at 800° C. for 1.5 hours. The solvent was removed under reduced pressure and the residual mass was dissolved in methylene chloride, washed successively with water, dried and concentrated to give 1.78 gm (86.4%) of pure 2,2,2-trichloroethyl-7α-methoxy-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide as a white solid.

NMR (CDCl3) δ 2.20 (s, 3H), 3.60 (s, 3H), 4.80 (d, 1H, J = 14 Hz), 4.90 (bs, 1H), 5.20 (d, 1H, J = 14 Hz), 5.30 (bs, 1H), 6.23 (d, 1H), 6.75 (d, 1H).

STEP H: Preparation of 2,2,2-trichloroethyl-7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate 1,1-dioxide

2,2,2-Trichloroethyl-7α-methoxy-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (1.78 g, 4.399 mmol) was dissolved in methylene chloride (70 ml). To this solution diphenyl diazomethane (0.940 g, 4.839 mmol) was added and the mixture was stirred at room temperature for 3 hours. After removal of the solvent the pink foam was purified over silica column using methylene chloride as eluant: 900 mg (35-8%).

NMR (CDCl3) δ 2.16 (s, 3H), 2.40 (d, 1H, J = 7.0 Hz), 3.0 (d, 1H, J = 7.0 Hz), 3.47 (d, 1H, J = 4.8 Hz, 1H, J = 12 Hz), 5.02 (d, 1H), 5.07 (d, 1H), 5.23 (d, 1H, J = 12 Hz).

EXAMPLE 9
Benzhydryl 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

STEP A: Preparation of 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide

2,2,2-Trichloroethyl 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (from Step H, Example 8, 2.39 g, 4.187 mmol) was dissolved in 50 ml of glacial acetic acid, zinc powder (7.0 g) was added and the mixture was stirred at room temperature for 1 hour, excess zinc was removed by filtration through a bed of Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, brine, dried and concentrated to give 1.5 g (83%) of pure acid.

NMR (CDCl3) δ 1.23 (s, 3H), 2.38 (d, 1H, J = 6.8 Hz), 2.94 (d, 1H, J = 6.8 Hz), 3.47 (s, 3H), 5.026 (bs, 1H), 5.054 (bs, 1H), 7.24-7.49 (m, 10H, aromatic).

STEP B: Preparation of benzhydryl 7α-methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

To a stirred solution of 7α-methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (830 mg, 1.889 mmol) in 20 ml of methylene chloride was added diphenyl diazomethane (367 mg, 1.889 mmol) and the mixture was stirred at room temperature for 3 hours, washed with dilute sodium bicarbonate solution, brine, dried and concentrated to give 1.3 g of the crude product which was purified over silica column using methylene chloride as eluant to give 362 mg of pure benzhydryl 7α-methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide.

NMR (CDCl3) δ 0.96 (s, 3H), 2.31 (d, 1H, J = 6.9 Hz), 2.92 (d, 1H, J = 6.9 Hz), 3.44 (s, 3H), 4.95 (d, 1H, J = 1.5 Hz), 5.05 (d, 1H, J = 1.5 Hz), 7.01 (s, 1H), 7.2-7.47 (m, 20 H, aromatic).

EXAMPLE 10
7α-Methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-pyrrolidine carboxamide-1,1-dioxide

7α-Methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (1.84 g, 4.187 mmol, from Step A, Example 9) was dissolved in 45 ml of methylene chloride, oxalyl chloride (797 mg, 6.280 mmol) was added followed by a drop of N,N-dimethyl formamide. The mixture was stirred at room temperature for one hour. Solvent was removed under reduced pressure and the light brown solid was dried under high vacuum.

The solid was redissolved in dry methylene chloride (15 ml), cooled in an ice-bath, and a solution of pyrrolidine (596 mg, 8.374 mmol) in dry methylene chloride (8 ml) was added dropwise. The mixture was stirred at ice temperature for 1 hour, washed with cold water, dilute hydrochloric acid, water, brine, dried and concentrated to give 1.57 g of the crude product which was purified over a silica column using hexane-ethyl acetate (1:1) as eluant to give pure, 1.04 (50.5%), 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-pyrrolidinecarboxamide-1,1-dioxide; crystallization from ether gave a pale yellow solid, mp. 222° C. (decomposed).

NMR (CDCl3) δ 0.92 (s, 3H), 1.71-2.04 (m, 4H, pyrrolidine), 2.23 (d, 1H, J = 6.7 Hz), 2.91 (d, 1H, J = 6.7 Hz), 3.09-3.68 (m, 4H, pyrrolidine), 3.46 (s, 3H), 4.94 (d, 1H, J = 1.5 Hz), 5.05 (d, 1H, J = 1.5 Hz), 7.17-7.50 (m, 10H, aromatic).

EXAMPLE 11
7α-Methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-piperidine carboxamide-1,1-dioxide

7α-Methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (1.0 g, 4.187 mmol, from Step A, Example 9) was dissolved in dry methylene chloride (15 ml), cooled in an ice-bath, washed with dilute hydrochloric acid, water, brine, dried and concentrated to give 1.57 g of the crude product which was purified over a silica column using hexane-ethyl acetate (1:1) as eluant to give pure, 1.04 (50.5%), 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-piperidinecarboxamide-1,1-dioxide; crystallization from ether gave a pale yellow solid, mp. 222° C. (decomposed).
2.275 mmol, from Step A, Example 9) was dissolved in 5 ml of methylene chloride, oxalyl chloride (0.3 ml, 3.413 mmol) was added followed by a drop of N,N-dimethyl formamide. The mixture was stirred at room temperature for one hour. Solvent was removed under reduced pressure.

The light brown solid was redissolved in dry methylene chloride (5 ml), cooled in an ice-bath, piperidine (388 mg, 4.551 mmol) dissolved in 5 ml of dry methylene chloride was added dropwise and the reaction mixture was stirred at ice-temperature for 2 hours, washed with water, brine, dried and concentrated to give 980 mg of crude product which was purified on a silica column using hexane ethyl acetate (2:1) as eluant to give 491 mg (42-66%) of pure 7a-methoxy-2-spiro (2,2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-piperidine carboxamide-1,1-dioxide.

NMR (CDCl3) δ 0.903 (s, 3H), 1.46-1.68 (m, 6H, piperidyl), 2.23 (d, 1H, J = 6.8 Hz), 2.91 (d, 1H, J = 6.8 Hz), 3.34-3.64 (m, 4H, piperidyl), 3.459 (s, 3H, OCH3), 4.95 (d, 1H, J = 1-5 Hz), 5.04 (d, 1H, J = 1.5 Hz), 7.20-7.50 (m, 10H, aromatic).

EXAMPLE 12
Benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-dichloro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

STEP A: Preparation of di(4-chlorophenyl)diazomethane

To a stirred ice-cold solution of 4,4'-dichlorobenzophenone hydrazine (1.303 g) in dry orylene chloride (20 ml) was added magnesium sulfate (590 mg), silver oxide (1.196 g) was added in one portion followed by potassium carbonate (30 mg). The mixture was stirred at ice-temperature for 1 hour, then at room temperature for an additional hour, filtered through Celite to give a dark purple solution which was directly used for the cyclodehydration reaction.

STEP B: Preparation of benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-dichloro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

Benzhydryl 7a-bromo-2-methylenem-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (2.0 g, from Step D, Example 2) was dissolved in dry methylene chloride (30 ml) and cooled in an ice-bath. To this solution di(4-chlorophenyl) diazomethane (from Step A) was added and the mixture was stirred at ice temperature for 1 hour. Evaporation of the solvent and purification over a silica column using hexane ethyl acetate mixture was eluant pure benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-dichloro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (1.2 g) was obtained, m.p. 202° C. (decomp.).

NMR (CDCl3) δ 1.03 (s, 3H), 2.32 (d, 1H, J = 7 Hz), 2.90 (d, 1H, J = 7 Hz), 4.94 (d, 1H, J = 1.5 Hz), 5.23 (d, 1H, J = 1.5 Hz), 7.03 (s, 1H, CHPh2), 7.18-7.42 (m, 15H, aromatic).

EXAMPLE 13
Benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-difluoro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

STEP A: Preparation of di(4-fluorophenyl)diazomethane

4,4'-Difluorobenzophenone (1.0 g, 4.306 mmol) was dissolved in methylene chloride (9 ml) containing iodine (0.2 ml, 1% w/v) and 1,1,3,3-tetramethyl guanidine (2.1 ml). To this solution was added peracetic acid solution (1.23 ml, 6.459 mmol) at 0° C. over 20 minutes. The mixture was stirred at 0° C. for 1 hour, then washed with water until the washings were at pH 6. The methylene chloride layer was dried over anhydrous sodium sulfate and concentrated to give a deep purple oil (850 mg, 83.7%) which was directly utilized for the next reaction.

STEP B: Preparation of benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-difluoro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

Benzhydryl 7a-bromo-2-methylenem-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (1.6 g, from step D, Example 2) was dissolved in dry methylene chloride (20 ml) and cooled in an ice-bath. To this solution di(4-fluorophenyl) diazomethane (from step A) was added and the mixture was stirred at ice-temperature for 1 hour. Evaporation of the solvent and purification over a silica column using hexanemethyl acetate mixture as eluant, pure benzhydryl 7a-bromo-2-spiro [2',2'-‘(4',4'-difluoro)diphenyl]cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (0.8 g) was obtained.

NMR (CDCl3) δ 1.04 (s, 3H), 2.33 (d, 1H, J = 7.2 Hz), 2.92 (d, 1H, J = 7.2 Hz), 4.92 (d, 1H, J = 1.5 Hz), 5.22 (d, 1H, J = 1.5 Hz), 6.88-7.44 (m, 18H, aromatic).

Following the procedure described in Example 13, Step B but starting with an appropriate diazo compound following the cyclopropyl derivatives were prepared:

(1) Benzhydryl 7a-bromo-2-spiro [2',2'-‘(2',2'-ethoxy carbonyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

NMR (CDCl3) δ 1.23 (t, 3H, COOCH2CH3), 1.80 (s, 3H, CH3), 2.18 (d, 2H, cyclopropyl, J = 8.5 Hz), 2.75 (t, 1H, CHCOOCH2CH3, J = 8.5 Hz), 4.17 (q, 2H, COOCH2CH3), 5.08 (d, 1H, J = 1.5 Hz), 3.26 (d, 1H, J = 1.5 Hz), 6.98 (s, 1H, CHPh2), 7.26-7.37 (m, 10H, aromatic).

(2) Benzhydryl 7a-bromo-2-spiro [2',2'-‘(2'-phennyl-2'-methyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

NMR (CDCl3) δ 0.92 (s, 3H, CH3), 1.78 (s, 3H, CH3), 2.23 (ABq, 2H, cyclopropyl, J = 7 Hz), 5.03 (d, 1H, J = 1.7 Hz), 5.34 (d, 1H, J = 1.7 Hz), 6.9 (s, 1H, CHPh2), 7.18-7.48 (m, 15H, aromatic).

(3) Benzhydryl 7a-bromo-2-spiro [2',2'-‘(2'-phenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

NMR (CDCl3) δ 1.07 (s, 3H, CH3), 2.09 (dd, 1H, cyclopropyl, J = 6.8 Hz and 8.0 Hz), 2.39 (dd, 1H, cyclopropyl, J = 6.8 Hz and 8.0 Hz), 3.29 (dd, 1H, cyclopropyl, J = 8.0 Hz and 10.0 Hz), 5.16 (d, 1H, J = 1.4 Hz), 5.45 (d, 1H, J = 1.4 Hz), 6.90 (s, 1H, CHPh2), 7.22-7.36 (m, 15H, aromatic).
EXAMPLE 14

Benzhydryl 7α-methoxy-2-spiro(2',2',-diphenyl)cyclopropyl 3-(1, 2, 3-triazolyl)methyl)-3-cephem-4-carboxylate-1,1-dioxide

STEP A: Preparation of 7β-amino-3-azidomethyl-3-cephem-4-carboxylic acid

To 7β-amino-3-azidomethyl-3-cephem-4-carboxylic acid (20.7 g, 81 mmol) in a mixture of dichloromethane (250 ml) and dimethyl sulfoxide (250 ml) was added dropwise a solution of diphenyldiazomethane (17.5 g, 90 mmol) in dichloromethane (150 ml).

The mixture was stirred at room temperature for 68 h, filtered, the filtrate was concentrated under reduced pressure. The residual sticky mass was taken in ethyl acetate (250 ml) and washed successively with saturated sodium bicarbonate solution, water, brine, dried over anhydrous sodium sulfate; solvent was removed under reduced pressure to yield a residue which was purified over a silica column using dichloromethane-ethyl acetate mixture (1:1) to give 18.4 g (54%) of a mixture of Δ2 and Δ3-cephems. The mixture was directly used for the next step without further separation.

STEP B: Preparation of benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate

To a suspension of 7β-amino-3-azidomethyl-3-cephem-4-carboxylic acid (20.7 g, 81 mmol) in dichloromethane (250 ml) and dimethyl sulfoxide (250 ml) was added dropwise a solution of diphenyldiazomethane (17.5 g, 90 mmol) in dichloromethane (150 ml). The mixture was stirred at room temperature for 68 h, filtered, the filtrate was concentrated under reduced pressure. The residual sticky mass was taken in ethyl acetate (250 ml) and washed successively with saturated sodium bicarbonate solution, water, brine, dried over anhydrous sodium sulfate; solvent was removed under reduced pressure to give a residue which was purified over a silica column using dichloromethane-ethyl acetate mixture (1:1) to give 18.4 g (54%) of a mixture of Δ2 and Δ3-cephems. The mixture was directly used for the next step without further separation.

STEP C: Preparation of benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide

To a stirred solution of the isomeric mixture of Δ2 and Δ3-cephems (from the step B, Example 14) (16 g, 38 mmol) in ethyl acetate (500 ml) at 0°C was added sodium tussinate dehydrate (1.254 g, 3.8 mmol) and hydrogen peroxide (30% solution, 17.5 ml). After stirring at 0°C for 15 min, the mixture was stirred at room temperature for 2 h when another batch of hydrogen peroxide (4.4 ml) was added and the resulting mixture was stirred overnight. The mixture was cooled in an ice-bath and sodium bisulfite solution (13 g in 100 ml of water) was added dropwise and the mixture was stirred for 10 min. Sodium carbonate solution (4 g in 80 ml of water) was added and the mixture was stirred for 10 min. Ethyl acetate layer was separated out, the aqueous layer was re-extracted with two portions of ethyl acetate. The combined ethyl acetate layer was washed with brine, dried (Na2SO4) and concentrated under reduced pressure. To the residue hexane was added and the mixture was stirred with ice-cooling. The precipitated solid was collected by filtration to give 12.2 g (71%) of pure benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide. IR (Nujol) max 2085, 1783, 1715 cm⁻¹.

STEP D: Preparation of benzhydryl 7α-methoxy-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide

To an ice-cooled stirred solution of benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (1.1 g, 2.43 mmol) in dichloromethane (15 ml) was added an ice-cool solution of sodium nitrite (184 mg, 2.67 mmol) in water (9 ml); 2.5 (N) sulfuric acid (1.1 ml) was added dropwise at such a rate that the temperature was below 0°C. The mixture was stirred at 0°C for 1 h, and the dichloromethane layer was separated out and the aqueous layer was re-extracted with dichloromethane (2×20 ml). The combined organic layer was washed with water (25 ml), brine (40 ml), dried (Na2SO4), filtered. To the filtrate, methanol (25 ml) was added and while stirring at room temperature, rhodium acetate dimer (12 mg) was added in one portion. After 1 h stirring at room temperature, the reaction mixture was filtered through Celite and solvent was removed under reduced pressure. The residue was purified by silica column using hexane-ethyl acetate mixture (3:2) as eluant to give 370 mg (33%) of pure benzhydryl 7α-methoxy-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide, m.p. 160°C-161°C. IR (Nujol) max 2090, 1791, 1716 cm⁻¹.

NMR (CDCl3) δ 3.56 (s, 3H), 3.71 and 3.99 (ABq, 2H, J = 18 Hz), 4.02 and 4.18 (ABq, 2H, J = 14 Hz), 4.70 (d, 1H, J = 15 Hz), 5.19 (d, 1H, J = 15 Hz), 6.97 (s, 1H), 7.31-7.46 (m, 10 H).

STEP E: Preparation of benzhydryl 7α-methoxy-3-(1, 2, 3-triazolyl)methyl)-3-cephem-4-carboxylate-1,1-dioxide

A solution of benzhydryl 7α-methoxy-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (3.1 g, 6.62 mmol) in ethylene glycol dimethyl ether (60 ml) was transferred to a steel bomb and cooled to −28°C; the reaction vessel was flushed with nitrogen for 15 min; 14.0 g of acetylene was taken in the steel bomb and the reaction mixture was heated at 90°C overnight. The steel bomb was cooled in an ice-bath and the excess acetylene was slowly allowed to evaporate at room temperature. Solvent was removed under reduced pressure. The crude product was purified on a silica column using hexane-ethyl acetate (1:1) as eluant to give a foamy product, 1.9 g (58%). Ether was added to the foam and solid separated out was filtered off, m.p. 123°-124°C. IR (Nujol) max 1786, 1713 cm⁻¹.

NMR (CDCl3) δ 3.55 (s, 3H), 3.65 and 3.97 (ABq, 2H, J = 18 Hz), 4.74 (s, 1H), 5.16 (s, 3H), 7.10 (s, 1H), 7.30-7.43 (m, 10 H), 7.51 (s, 1H), 7.67 (s, 1H).

STEP F: Preparation of benzhydryl 7α-methoxy-2-exomethyleno-3-(1, 2, 3-triazolyl)methyl)-3-cephem-4-carboxylate-1,1-dioxide

To a solution of benzhydryl 7α-methoxy-3-(1, 2, 3-triazolyl)methyl)-3-cephem-4-carboxylate-1,1-dioxide (1.8 g, 3.85 mmol) in dichloromethane (30 ml) and t-butanol (70 ml) was added dimethylamine hydrochloride (940 mg, 11.54 mmol) and formaldehyde solution (37%, 410 mg, 13.5 mmol). The mixture was heated at 80°C for 1.5 h and solvent was removed in vacuo. The residue was taken in dichloromethane (60 ml) and
washed with cold water, brine, dried and concentrated. The residue was purified by silica column using hexane-ethyl acetate (1:2) as eluant to give benzhydryl 7α-methoxy-2-oxomethylene-3-[(1, 2, 3-triazolyl)methyl]-3-cephem-4-carboxylate-1, 1-dioxide (910 mg, 49%); m.p. 177°-179° C, dec. (ethyl acetate-ether). IR (Nujol) max 1765, 1723 cm⁻¹.

NMR (CDCl₃) δ 3.57 (s, 3H), 4.87 (d, 1H, J = 2 Hz), 5.01 and 5.47 (ABq, 2H, J = 15 Hz), 5.29 (d, 1H, J = 2 Hz), 6.55 (d, 1H, J = 2.6 Hz), 6.64 (d, 1H, J = 2.6 Hz), 7.06 (s, 1H), 7.3-7.37 (m, 10H), 7.51 (s, 1H), 7.58 (s, 1H).

STEP G: Benzhydryl 7α-methoxy-2-spiro
(2', 2'-diphenyl) cyclopropyl-3-[(1, 2, 3-triazolyl)]
metyl]-3-cephem-4-carboxylate-1, 1-dioxide

To a stirred solution of benzhydryl 7α-methoxy-2-
oxomethylene-3-[(1.23-triazolyl)]methy]-
3-cephem-4-carboxylate-1, 1-dioxide (840 mg, 1.66 mmol) in dichloromethane (20 ml) at room temperature was added diphenylidiazomethane (390 mg, 2.01 mmol). The reaction mixture was stirred at room temperature for 1 h, solvent was removed under reduced pressure. The residue was purified by silica column chromatography using ethyl acetate-hexane (1:1) as eluant to give 600 mg (54%) of pure benzhydryl 7α-methoxy-2-spiro[(2', 2'-
diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-
cephem-4-carboxylate-1, 1-dioxide, m.p. 196°-198° C, dec. (ethyl acetate-hexane). IR (Nujol) max 1783, 1732 cm⁻¹.

NMR (CDCl₃) δ 2.55 and 2.75 (ABq, 2H, J = 7.6 Hz), 3.5 and 4.0 (ABq, 2H, J = 15 Hz), 3.47 (s, 3H), 5.0 (d, 1H, J = 2 Hz), 5.1 (d, 1H, J = 2 Hz), 7.06 (s, 1H), 7.24-7.49 (m, 20H), 7.63 (s, 1H), 7.9 (s, 1H).

EXAMPLE 15

7α-Methoxy-2-spiro[(2', 2'-diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-cephem-4-
carboxylic acid-1, 1-dioxide

Benzhydryl 7α-methoxy-2-spiro[(2', 2'-diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-cephem-4-
carboxylate-1, 1-dioxide (from Step G, Example 14, 220 mg, 0.327 mmol) was dissolved in anisole (2 ml) and dichloromethane (1 ml) and cooled in an icebath with stirring. After stirring at 0°C for 10 min, trifluoroacetic acid (3 ml) was added. The resulting mixture was stirred at 0°C for 1 h and solvent was removed to give an oil. A mixture of dry ether (5 ml) and hexane (5 ml) was added to the oil and the mixture was stirred with ice-cooling. The precipitated white solid was collected by filtration and dried over phosphorus pentoxide overnight to give 160 mg (97%) of 7-methoxy-2-spiro[(2', 2'-
diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-
cephem-4-carboxylic acid-1, 1-dioxide.

NMR (CDCl₃) δ 2.45 (d, 1H, J = 7.6 Hz), 2.81 (d, 1H, J = 7.6 Hz), 3.48 (s, 3H), 3.6 (d, 1H, J = 15 Hz), 4.76 (d, 1H, J = 15 Hz), 5.06 (d, 1H, J = 1.8 Hz), 5.09 (d, 1H, J = 1.8 Hz), 6.0 (br, s, 1H), 7.24-7.52 (m, 10H), 7.77 (s, 1H), 8.10 (s, 1H).

STEP B: 7β-Methoxy-2-spiro[(2', 2'-diphenyl) cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-cephem-4-
carboxylic acid-1, 1-dioxide

To an ice-cooled solution of 7α-methoxy-2-spiro-
[(2', 2'-diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]
metyl]-3-cephem-4-carboxylic acid-1, 1-dioxide (150 mg, 0.296 mmol) in dichloromethane (3 ml) was added oxalyl chloride (46 mg, 0.362 mmol) dissolved in dichloromethane (1 ml), dimethyl formamide (1 drop) was added and the reaction mixture was stirred at 0°C for 15 min. Followed by at room temperature for 15 min. Solvent was removed under reduced pressure and the residue was redissolved in dichloromethane (2 ml), cooled in an ice-bath, piperdine (58 mg, 0.68 mmol) in dichloromethane (1 ml) was added dropwise and the reddish brown solution was stirred at 0°C for 1 h. Solvent was removed under reduced pressure to give a crude product (240 mg) which was purified on a silica column using ethyl acetate-acetonitrile mixture (6:4) as eluant to give pure 7α-methoxy-2-spiro[(2', 2'-diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)]methy]-3-cephem-4-
icarboxylic acid-1, 1-dioxide.

NMR (CDCl₃) δ 1.63-2.09 (m, 6H, piperdine), 2.37 (d, 1H, J = 7.2 Hz), 3.01 (d, 1H, J = 7.2 Hz), 3.4730 (m, 6H, piperdine+3°-CH₃), 3.50 (s, 3H, OCH₃), 4.84 (d, 1H, J = 1.3 Hz), 4.86 (d, 1H, J = 1.3 Hz), 6.98-7.53 (m, 10H, aromatic), 7.87 (s, 1H), 8.10 (s, 1H).

EXAMPLE 16

p-Methoxybenzyl 7α-methoxy-2-spiro[(2', 2'-diphenyl] cyclopropyl-3-[(1, 2, 3-triazolyl)methyl]-3-cephem-4-
carboxylate-1, 1-dioxide

STEP A: Preparation of p-methoxybenzyl
7α-amino-3-azido-methyl-3-cephem-4-
carboxylate

p-Methoxybenzyl-7-amino-3-chloromethyl-3-cephem-
4-carboxylate (30.5 g, 0.083 mol) was dissolved in N,N-dimethylformamide (160 ml). A solution of sodium azide (26.8 g, 0.414 mol) in water (75 ml) was added dropwise over a period of 15 min to the above solution and the dark brown reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with methylene chloride and the organic layer was separated, washed successively with water, brine, dried (Na₂SO₄) and concentrated in vacuo to give a dark brown residue (25 g) which was purified over silica column using a mixture of hexane-ethyl acetate (3:1) as eluant to give pure p-methoxybenzyl 7β-amino-
3-azidomethyl-3-cephem-4-carboxylate (17.5 g, 52.5%)
IR (Nujol) max 2105 cm⁻¹.

NMR (CDCl₃) δ 8.10 (br, 2H, NH₂), 3.47 (ABq, 2H, J = 18 Hz), 3.81 (s, 3H, OCH₃), 3.93 and 4.34 (ABq, 2H, J = 13.7 Hz), 4.75 (d, 1H, J = 5.1 Hz), 4.91 (d, 1H, J = 5.1 Hz), 5.23 (s, 2H, —COOCH₂), 6.89 (d, 2H, aromatic), 7.35 (d, 2H, aromatic).

STEP B: Preparation of p-methoxybenzyl
7α-amino-3-azido-methyl-3-cephem-4-carboxylate-1,
1-dioxide

p-Methoxybenzyl 7β-amino-3-azidomethyl-3-cephem-
4-carboxylate (17.15 g, 0.046 mol) in ethylacetate was cooled to 15°C, sodium tungstate dehydrate (1.52 g, 0.0046 mol) was added followed by hydrogen peroxide (30%, 20.73 ml) in one portion and the stirring was continued at room temperature. After two hours an additional portion of hydrogen peroxide (5.18 ml) was
added and the reaction mixture was stirred at room temperature for a total period of 18 h; the mixture was cooled to 10°C and a solution of sodium sulphite (10%, 600 ml) was added while stirring. Organic layer was separated out, washed withaq. sodium bicarbonate solution, brine and dried (Na2SO4). Evaporation of the solvent in vacuo gave a foam (12 g) which was purified over a silica column using hexane-ethyl acetate (1:3) as eluant to give the pure product as a white foam (6.8 g, 36.5%). IR (Nujol) max 2083 cm⁻¹.

NMR (CDCl3) δ 2.23 (br s, 2H, NH2), 3.71 and 3.92 (ABq, 2H, J = 18 Hz, CH2N), 3.81 (s, 3H, OCH3), 4.11 and 4.34 (ABq, 2H, J = 14 Hz), 4.72 (d, 1H, J = 4 Hz), 4.89 (d, 1H, J = 4 Hz), 5.24 (s, 2H, —COOCH2), 6.90 (d, 2H, aromatic), 7.39 (d, 2H, aromatic).

STEP C: Preparation of p-methoxybenzyl 7β-amino-3-(1,2,3-triazolyl) methyl]-3-cephem-4-carboxylate-1,1-dioxide

p-Methoxybenzyl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (2.7 g, 0.0066 mol) was dissolved in ethylene glycol dimethyl ether (100 ml) and placed in a steel bomb. The reaction vessel was cooled to -60°C and charged with 3.0 g of acetylene. The steel bomb was heated at 90°C over a period of 8 h. Excess acetylene was carefully vented out at 0°C and the solvent was removed in vacuo to give a crude mass (2.0 g) which was purified on a silica column using hexane-ethyl acetate (3:7) as eluant to give pure p-methoxybenzyl-7α-amino-3-(1,2,3-triazolyl) methyl]-3-cephem-4-carboxylate-1,1-dioxide (1.45 g, 50.52%).

NMR(CDCl3) δ 2.04 (br, 2H, NH2), 3.59 and 3.96 (ABq, 2H, J = 18.3 Hz), 3.80 (s, 3H, OCH3), 4.64 (br, s, 1H), 4.87 (br, s, 1H), 5.04–5.36 (m, 4H), 5.02 (d, 2H, aromatic), 7.31 (d, 2H, aromatic), 7.68 (s, 2H, triazole).

STEP D: Preparation of p-methoxybenzyl-7α-amino-3-(1,2,3-triazolyl) methyl]-3-cephem-4-carboxylate-1,1-dioxide

A solution of p-methoxybenzyl-7β-amino-3-(1,2,3-triazolyl) methyl]-3-cephem-4-carboxylate-1,1-dioxide (800 mg, 0.00185 mol) in dry ethyl acetate was cooled to 10°C under nitrogen. Isopropyl nitrite (0.247 g, 0.0028 mol) was added to the above solution followed by 3 drops of trifluoroacetic acid. The reaction mixture was further stirred at 10°C for 1 h and cooled to -5°C. Rhodium octanoate dimer (18 mg) was dissolved in a mixture of ethyl acetate (10 ml) and anhydrous methanol (2 ml) and the mixture was stirred under nitrogen at 0°C. After stirring for 30 min, 5 drops of triethylamine was added (the color changes from light green to purple) and the solution was further cooled to -5°C. The above two solutions were mixed together at -5°C and stirred for 2 h. The reaction mixture was diluted with 50 ml of ethylacetate, made acidic with glacial acetic acid, the reaction mixture was washed with cold water, brine, dried over anhydrous sodium sulfate. Evaporation of the solvent gave a dark brown foam which was purified over silica column using hexane-ethyl acetate (1:1) as eluant to give the desired product, p-methoxybenzyl-7α-amino-3-(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide, 140 mg (20%).

NMR(CDCl3) δ 3.54 (s, 3H, OCH3), 3.65 and 3.93 (ABq, 2H, J = 18 Hz), 3.82 (s, 3H, OCH3), 4.70 (d, 1H, J = 1.1 Hz), 5.08–5.40 (m, 5H), 6.91 (d, 2H, aromatic), 7.37 (d, 2H, aromatic), 7.73 (s, 2H, triazole).
successively with water, dil. hydrochloric acid and brine; dried (Na$_2$SO$_4$) and concentrated to give a light brown foam (0.42 g) which was purified on column using hexane-ethyl acetate mixture as eluant to give pure 7α-methoxy-2-spiro(2',2'-diphenyl)-cyclopropyl-3-methyl-3-cephem-4-[4-carboxy piperidine carboxamido]-1,1-dioxide as a white foam (0.011 g).

NMR(CDC$_3$) δ 1.28 (s, 3H, CH$_3$), (s, 9H, t-butyl), 1.92–2.20 (m, 4H, pyrrolidinyl), 2.26 (d, 1H, J = 7.0 Hz), 2.80 (d, 1H, J = 6.92 Hz), 3.40–3.49 (m, 1H, pyrrolidinyl), 3.43 (s, 3H, OCH$_3$), 3.61–3.71 (m, 1H, pyrrolidinyl), 4.41–4.46 (br, dd, 1H, pyrrolidinyl), 4.53 (d, 1H, J = 1.85 Hz), 4.74 (d, 1H, J = 1.87 Hz), 7.15–7.48 (m, 10H, aromatic).

**EXAMPLE 18**

7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-[N-methyl piperazine carboxamido]-1,1-dioxide

To a stirred and ice-cooled solution of 7α-methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (0.439 g, from Step A, Example 9), in dry dichloromethane (5 ml) was added oxalyl chloride (0.1 ml) followed by two drops of N,N-dimethyl formamide, the mixture reaction was stirred at ice-temperature for 15 min and at room temperature for 15 min. Solvent was removed under reduced pressure. The residue was redissolved in dry dichloromethane (5 ml), cooled in an ice-bath, N-methyl piperazine (0.22 ml) was added in one portion and the reaction mixture was stirred at ice-temperature for 1 h. The reaction mixture was diluted with methylene chloride, washed with ice-cold water, dil. hydrochloric acid and finally with brine, dried (Na$_2$SO$_4$) and concentrated to give brown foam which was purified on silica column using hexane-ethyl acetate mixture as eluant to give 0.32 g of pure product which was crystallized from ether to give a pale yellow solid (0.192 g), m.p. 202–204°C.

1H NMR(CDC$_3$) δ 0.89 (s, 3H, CH$_3$), 2.24 (d, 1H, J = 7.07 Hz), 2.28 (s, 3H, N-CH$_3$), 2.36–2.54 (m, 4H, piperoxazinyl), 2.91 (d, 1H, J = 7.07 Hz), 3.46 (s, 3H, OCH$_3$), 3.49–3.62 (m, 3H, piperoxazinyl), 3.77–3.85 (m, 1H, piperoxazinyl), 4.95 (d, 1H, J = 2.05 Hz), 5.05 (d, 1H, J = 2.09 Hz), 7.17–7.70 (m, 10H, aromatic).

**EXAMPLE 19**

7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-[4-t-butoxy carbonyl piperidine carboxamido]-1,1-dioxide

7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (1.87 g, 6.53 mmol) was taken in dry methylene chloride (40 ml), oxalyl chloride (1.10 g) was added followed by two drops of dimethyl formamide. The reaction mixture was stirred at ice-temperature for 15 min and then at room temperature for 4 hours. Solvent was removed under reduced pressure, the residue was dissolved in methylene chloride (50 ml) and evaporated again in vacuo. The residue was redissolved in methylene chloride (50 ml), cooled to 0°C; a solution of t-butyli isonippecotate (1.21 g, 6.53 mmol) in dry methylene chloride (50 ml) was added followed by triethylamine (0.667 g, 6.53 mmol). The reaction mixture was stirred at 0°C for 30 min and at room temperature for 2.5 hours. After the reaction was complete, the reaction mixture was diluted with methylene chloride (100 ml) and washed successively with water, 1(N) HCl acid, water, aq. NaHCO$_3$ solution, brine, dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure gave a foam (4.1 g) which was purified over a silica gel column using hexane-ethyl acetate mixture (1:1) as eluant to give a white foam (3.39 g, 83.96%).

1H NMR (200 MHz, CDC$_3$): δ 0.89 and 0.92 (2s, 3H), 1.42 and 1.44 (2s, 9H), 1.51–2.03 (m, 4H, piperoxidyl), 2.24 (d, 1H, J = 7.0 Hz), 2.37–2.47 (m, 1H, piperoxidyl), 2.91 (d, 1H, J = 7.0 Hz), 2.97–3.11 (m, 2H, piperoxidyl), 3.45 (s, 3H), 3.64–3.79 (m, 1H, piperoxidyl), 4.34–4.41 (m, 1H, piperoxidyl), 4.96 (br, s, 1H), 5.03–5.06 (m, 1H), 7.17–7.50 (m, 10H).

**EXAMPLE 20**

7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-[4-carboxy piperidine carboxamido]-1,1-dioxide

A solution of 7α-methoxy-2-spiro(2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-t-butoxy carbonyl piperidine carboxamido]-1,1-dioxide (4.4 g, 7.3 mmol) in anhydrous formic acid (70 ml) was heated to 105°C for 2 hours. After the completion of the reaction the reaction mixture was freeze-dried to give a white solid which was washed thoroughly with a mixture of hexane-ether (4:1), the solid was collected by filtration and air dried (3.78 g, 94.74%).

1H NMR (200 MHz, CDCl$_3$+DMSO-d$_6$) δ 0.87 and 0.90 (2s, 3H), 1.58–2.05 (m, 4H, piperoxidyl), 2.26 (d, 1H, J = 6.70 Hz), 2.49–2.51 (m, 1H, piperoxidyl), 2.90 (d, 1H, J = 6.70 Hz), 3.03–3.14 (m, 2H, piperoxidyl), 3.46 (s, 3H), 3.63–3.82 (m, 1H, piperoxidyl), 5.00 (br, s, 1H), 5.04 (br s, 1H), 7.21–7.48 (m, 10H), 11.90 (br s, 1H).

**EXAMPLE 21**

7α-Methoxy-2-spiro(2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[2-[N-t-butylpropionate-2-yl] carboxamido]pyrrolidine carboxamido]-1,1-dioxide

To a stirred and ice cooled solution of 7α-methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (365 mg, 0.83 mmol) in methylene chloride (15 ml) was added oxalyl chloride (140 mg, 1.08 mmol) followed by two drops of DMF. The suspension became clear within 5 minutes. The reaction mixture was stirred at ice-temperature for 15 min and at room temp. for 30 min. Then it was evaporated in vacuo to give a pink colored solid. The solid was redissolved in DCM and evaporated in vacuo. The solid thus obtained was dissolved in DCM (10 ml) and cooled to 0°C. Under nitrogen atmosphere. A solution of Pro-Ala-tert-butyl ester (201 mg, 0.83 mmol) in DCM (3 ml) was added to the above reaction mixture followed by triethylamine (85 mg, 0.83 mmol) dissolved in 2 ml of DCM. The above reaction mixture was stirred at 0°C for 15 min at room temp. for 3 hours. The reaction mixture was diluted with 100 ml of DCM and washed successively with cold water, aq. NaHCO$_3$ solution, brine, dried over anhydrous Na$_2$SO$_4$ and evaporated to give a light green colored foam (480 mg) which was purified over a silica gel column using a mixture of hexane-ethyl acetate (1:1) as eluant. The compound obtained (310 mg) was further purified by preparative tlc using a mixture of methylene chloride-ethyl acetate (8:2) as developing solvent. The purified product was used in Example 22.
EXAMPLE 22

7α-Methoxy-2-spiro(2′,2′′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxamido]-pyrrolidine carboxamide, 1,1-dioxide

A solution of 7α-methoxy-2-spiro[2′,2′′-diphenylcyclopropyl-3-methyl-3-cephem-4]-[N-(1-t-butyloxycarbonyl-3-methyl-butan-1-yl)]-carboxamido] pyrrolidine carboxamide, 1,1-dioxide (104 mg, 0.16 mmol) in anhydrous formic acid (9 ml) was stirred at room temperature for 2 hours and freeze-dried (93 mg). 1H NMR (200 MHz, CDCl₃): 860.90 (s, 3H, CH₃), 1.49 (d, 3H, J = 1.13 Hz), 1.81-2.19 (m, 2H, pyrroldi- nyll), 2.22-2.28 (m, 3H, cyclopropyl + pyrrolidinyl), 2.95 (d, 1H, J = 6.94 Hz, cyclopropyl), 3.33-3.58 (m, 5H, CH₂O + pyrrolidinyl), 4.52-4.65 (m, 2H, pyrrolidinyl), 5.11 (d, 1H, J = 1.96 Hz), 5.13 (d, 1H, J = 1.96 Hz), 7.19-7.52 (m, 11H, aromatic + COOH), 7.90 (d, 1H, J = 7.28 Hz, NH).

EXAMPLE 23

7α-Methoxy-2-spiro(2′,2′′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-[N-(1-t-butyloxycarbonyl-3-methyl-butan-1-yl)]carboxamido-1,1-dioxide

To a stirred and ice-cooled solution of 7α-methoxy-2-spiro[2′,2′′-diphenylcyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (130 mg, 270 mmol) in methylene chloride (50 ml) was added oxalyl chloride (263 mg, 20.3 mmol) followed by two drops of DMF. The reaction mixture was stirred at 10°C for 15 min and at room temperature for 45 min and then it was evaporated in vacuo. The residue thus obtained was dissolved in methylene chloride and evaporated again in vacuo. The residue was finally dissolved in anhydrous methylene chloride (50 ml) and cooled to 5°C under N₂, to the above solution a solution of 2-iodobenzene-1-sulfonyl chloride 127 (307 mg, 1.64 mmol) in methylene chloride (2 ml) was added followed by a solution of triethylamine (175 mg, 1.72 mmol) in methylene chloride (1 ml). The reaction mixture was stirred at 5°C for 15 min, then at room temperature for 3 hours, diluted with methylene chloride (100 ml) and washed successively with water, 1N HCl acid, water, 1N NaHCO₃ solution, brine, and dried over anhydrous Na₂SO₄ and evaporated in vacuo to give yellow colored foam (800 mg) which was purified over a silica gel column using a mixture of hexane-ethyl acetate (3:2) to give the product as a white solid (590 mg, 62.17%). 1H NMR (200 MHz, CDCl₃): 8 0.95 (d, 6H, J = 6.13 Hz), 1.07 (s, 3H), 1.49 (s, 9H), 1.57-1.80 (m, 3H), 2.31 (d, 1H, J = 7.0 Hz), 2.92 (d, 1H, J = 7.0 Hz), 3.46 (s, 3H), 4.6 (q, 1H), 4.92 (d, 1H, J = 2.0 Hz), 5.03 (d, 1H, J = 2.0 Hz), 6.44 (d, 1H, J = 8.1 Hz), 7.21-7.47 (m, 10H).

EXAMPLE 24

7α-Methoxy-2-spiro(2′,2′′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-[N-(1-carboxy-3-methyl-butan-1-yl)]carboxamido-1,1-dioxide

A solution of 7α-methoxy-2-spiro[2′,2′′-diphenylcyclopropyl-3-methyl-3-cephem-4]-[N-(1-t-butyloxycarbonyl-3-methyl-butan-1-yl)]carboxamido, 1,1-dioxide (170 mg, 0.28 mmol) in anhydrous formic acid (15 ml) was stirred at room temperature for 2 hours. The progress of the reaction was followed by TLC when all the starting material was completely disappeared. The reaction mixture was freeze-dried to give a white solid which was washed thoroughly with a mixture of hexane-ether (9:1). The solid was collected by filtration and air dried (153 mg, 99.35%). 1H NMR (200 MHz, CDCl₃): 8 0.95 (d, 6H, J = 1.41 Hz), 1.07 (s, 3H), 1.75 (br, s, 3H), 2.33 (d, 1H, J = 7.0 Hz), 2.93 (d, 1H, J = 7.0 Hz), 3.46 (s, 3H), 4.74 (br, s, 1H), 4.97 (br, s, 1H), 5.04 (br, s, 1H), 6.71 (br d, 1H), 7.26-7.47 (m, 10H).

EXAMPLE 25

7α-Methoxy-2-spiro(2′,2′′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-(N-methyl piperazine carboxamido)-1,1-dioxide

To a stirred and ice-cooled solution of 7α-methoxy-2-spiro[2′,2′′-diphenylcyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (0.439 g, from Step A, Example 9), in dry dichloromethane (5 ml) was added oxalyl chloride (0.1 ml) followed by two drops of N,N-dimethyl formamide, the reaction mixture was stirred at ice-temperature for 15 min and at room temperature for 15 min. Solvent was removed under reduced pressure. The residue was redissolved in dry dichloromethane (5 ml), cooled in an ice-bath, N-methyl piperazine (0.22 ml) was added in one portion and the reaction mixture was stirred at ice-temp, for 1 h. The reaction mixture was diluted with methylene chloride, washed with ice-cold water, dil. hydrochloric acid and finally with brine, dried (Na₂SO₄) and concentrated to give a brown foam which was purified on silica gel column using hexane-ethyl acetate mixture as eluant to give 0.32 g of pure product which was crystallized from ether to give a pale yellow solid (0.192 g), m.p. 202°-204°C. 1H NMR (CDCl₃): 8 0.89 (s, 3H, CH₃), 2.24 (d, 1H, J = 7.07 Hz), 2.28 (s 3H, N-CH₃), 2.36-2.54 (m, 4H, piperazinyl), 2.91 (d, 1H, J = 7.07 Hz), 3.46 (s, 3H, OCH₃), 3.49-3.62 (m, 3H, piperazinyl), 3.77-3.85 (m, 1H, piperazinyl), 4.93 (d, 1H, J = 2.05 Hz), 5.05 (d, 1H, J = 2.09 Hz), 7.17-7.50 (m, 10H, aromatic).

EXAMPLE 26

7α-Methoxy-2-spiro(2′,2′′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-(4-tert-butoxycarbonyl-piperazinyl)piperazine carboxamido-1,1-dioxide

To a stirred and ice cooled suspension of 7α-methoxy-2-spiro[2′,2′′-diphenylcyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (1.0 g, 2.28 mmole) in methylene chloride (50 ml) was added oxalyl chloride (0.347 g, 2.74 mmole) followed by two drops of DMF. The suspension became clear after a few minutes. The reaction mixture was stirred at ice-bath temperature for 10 min and at room temperature for 1.5 h at which time the solvent was removed in vacuo. The residue was dissolved in methylene chloride (40 ml) and solvents were removed in vacuo. The last step was repeated with another 40 ml of methylene chloride and then the flask was placed on the pump to remove any residual oxalyl chloride. The solid obtained was dissolved in methylene chloride (40 ml) and cooled to 0°C under nitrogen atmosphere. A solution of tert-butoxycarbonyl piperazine (0.51 g, 2.74 mmole) in methylene chloride (10 ml) was added to the above reaction mixture followed by triethylamine (0.277 g, 2.74 mmole). After stirring at ice-bath temperature for 10 min, the mixture was stirred at room temperature for 2.5 h. Methylene chloride (50 ml) was added to the reaction mixture and washed successively with aqueous sodium bicarbonate.
bicarbonate (5%, 20 mL) solution; water and brine. The methylene chloride solution was dried (Na$_2$SO$_4$) and solvent was removed in vacuo to give a foam (1.6 g) which was purified over a silica gel column using a mixture of hexane-ethyl acetate (1:2) as eluant to give 1.0 (72%) of product.

1H NMR (200 MHz, CDCl$_3$) δ 0.89 (s, 3H, CH$_3$); 1.44 (s, 9H, t-buty1); 2.24 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.92 (d, 1H, J = 7.0 Hz, cyclopropyl); 3.38-3.82 (m, 8H, piperazine); 3.46 (s, 3H, OCH$_3$); 4.96 (d, 1H, J = 1.9 Hz); 5.04 (d, 1H, J = 1.9 Hz); 7.21-7.49 (m, 10H, aromatic).

IR (Nujol): max 1777, 1685, 1642 cm$^{-1}$

**EXAMPLE 27**

7α-Methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-piperazine carboxamide-1,1-dioxide

A solution of 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-tert-butoxycarbonyl] piperazine carboxamide-1,1-dioxide (100 mg, 0.16 mmol) in anhydrous formic acid (3 mL) was stirred in a warm water bath (35°C) for 1.5 h and freeze dried to give 100 mg of crude product. The residue was purified on a silica gel column eluting with a solvent gradient of hexane-ethyl acetate (1:3), ethyl acetate and finally with ethyl acetate-methanol (4:1) to give 60 mg (72%) of a solid. The solid was dissolved in a minimum amount of methylene chloride and hexane was added to give 20 mg of pure product.

1H NMR (200 MHz, CDCl$_3$) δ 0.90 (s, 3H, CH$_3$); 1.93 (br, s, piperazine); 2.24 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.91 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.7-3.05 (m, 3H, piperazine); 3.46 (s, 3H, OCH$_3$); 3.3-3.85 (m, 5H, piperazine); 4.96 (d, 1H, J = 2 Hz); 5.04 (d, 1H, J = 2 Hz); 7.21-7.5 (m, 10H, aromatic).

IR (Nujol): max 1778, 1636 cm$^{-1}$

**EXAMPLE 28**

7α-Methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-tert-butoxy carbonyl methyl] piperazine carboxamide-1,1-dioxide

To a stirred and ice cooled suspension of 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-tert-butoxy carbonyl methyl] piperazine carboxamide-1,1-dioxide (400 mg, 0.91 mmol) in methylene chloride (20 mL) was added oxalyl chloride (139 mg, 1.09 mmol) followed by two drops of DMF. The reaction mixture was stirred at ice-bath temperature for 10 min and at room temperature for 1.5 h during which time the carbonyl acid dissolved completely. The solvent was removed in vacuo and the resulting solid was redissolved twice in methylene chloride (2×20 mL) and solvent was removed in vacuo each time. The residue was placed on the pump for 40 minutes to remove any remaining oxalyl chloride. The solid obtained was dissolved in methylene chloride (20 mL) and cooled to 0°C under a nitrogen atmosphere. A solution of t-butoxy-carbonyl methyl piperazine (220 mg, 1.09 mmol) in methylene chloride (15 mL) was added followed by triethylamine (111 mg, 1.09 mmol). After stirring at ice-bath temperature for 10 mins, the reaction mixture was stirred at room temperature for 2 h. Methylene chloride [50 mL] was added to the reaction mixture and then washed successively with dilute HCl [0.5 N], 15 mL, NaHCO$_3$ [5%, 15 mL] solution, water and brine. The methylene chloride solution was dried (Na$_2$SO$_4$) and solvent was removed in vacuo to give 0.65 g of foam. Purification on a silica gel column using hexane-ethyl acetate (1:2, v/v) as eluant gave 350 mg (56%) of product.

1H NMR (200 MHz, CDCl$_3$) δ 0.89 (s, 3H, CH$_3$); 1.45 (s, 9H, t-buty1); 2.24 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.91 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.54-2.63 (m, 4H, piperazine); 3.12 (s, 2H, CH$_2$); 3.46 (s, 3H, OCH$_3$); 3.12-3.61 (m, 3H, piperazine); 3.86-3.92 (m, 1H, piperazine); 4.95 (d, 1H, J = 1.9 Hz); 5.03 (d, 1H, J = 1.9 Hz); 7.17-7.49 (m, 10H, aromatic).

**EXAMPLE 29**

7α-Methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-N-acetic acid] piperazine carboxamide-1,1-dioxide

A stirred solution of 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-[4-tert-butoxy carbonyl methyl] piperazine carboxamide-1,1-dioxide (190 mg, 0.305 mmol) in anhydrous formic acid (30 mL) was placed in a warm water bath (40°C). The mixture was stirred overnight during which time the temperature was allowed to drop to room temperature. The resulting mixture was freeze dried and the solid obtained was dissolved in a minimum amount of dichloromethane. Ether and hexane were added to precipitate 35 mg of pure product.

1H NMR (200 MHz, CDCl$_3$) δ 0.89 (s, 3H, CH$_3$); 2.25 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.92 (d, 1H, J = 7.0 Hz, cyclopropyl); 2.72-2.80 (m, 4H, piperazine); 3.26 (s, 2H, CH$_2$); 3.46 (s, 3H, OCH$_3$); 3.43-4.03 (m, 5H, piperazine+COOH); 4.96 (d, 1H, J = 1.9 Hz); 5.03 (d, 1H, J = 1.9 Hz); 7.22-7.49 (m, 10H, aromatic).

What is claimed is:

1. A 2-spiro cyclopropyl cephalosporin sulfone compound of formula I:

wherein

R$_1$ is OR$_6$;

R$_2$ is hydrogen, halogen, hydroxy, C$_4$-alkyl, C$_4$-alkoxy, C$_2$-6 alkenyl, C$_2$-6 alkyl, or CH$_2$ X, wherein X is hydrogen, halogen, acetate, a triazoyl group, a quaternary ammonium group selected from the group consisting of pyridinium group, N-methyl pyridinium group, and N-methyl piperidinium group, or CH$_2$ YR$_9$, wherein Y is oxygen, sulfur or nitrogen, and when Y is oxygen, S$_9$ is hydrogen or a C$_4$-6 alkyl group, and when Y is sulfur, R$_9$ is a phenyl group or a 5 to 6 membered heterocyclic group containing 1 to 4 nitrogen atoms, or with sulfur or oxygen, wherein the heterocyclic ring can be further substituted with a methyl group, a hydroxy group, a carboxy group, or —CH$_2$COOH, and when Y is nitrogen, R$_9$ is H, C$_4$-6, or phenyl;

R$_3$ and R$_4$, which are the same or different, are hydrogen, C$_4$-6 alkyl group, halo C$_4$-6 alkyl, C$_6$-10 aryl, halo C$_6$-10 aryl, C$_3$-$C_4$ cycloalkyl, hydroxy C$_4$-6 alkyl, C$_4$-6 alkoxy C$_4$-6 alkyl, a—CH$_2$COOH group, a —COOH group, a COOC$_4$-6 alkyl group, a
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—CH₂COOC₁₆₆ alkyl group; or a 5 to 6 membered heterocyclic group containing at least one heteroatom selected from the group consisting of O,S, and N;
R₃ is hydrogen, halogen, methoxy, ethoxy, methylsulfonamide, trifluoromethyl sulfonamide, methanesulfonyloxy, or trifluoromethane sulfonfolyx;
R₄ is hydrogen, C₁₆₆ alkyl, C₂₆₆ alkenyl, C₃₆₆ alkynyl, C₄₆₆ alkanoyl C₅₆₆ alkyl, C₆₆₆ alkanoyloxy C₇₆₆ alkylichlo, C₈₆₆ alkoxy C₉₆₆ alkenyl, C₁₀₆₆ cycloalkyl, halogenated C₁₁₆₆ alkyl, a phenyl, —CH₂—(phenyl), —CH(phenyl)₂, wherein the phenyl group may be substituted with at least one of C₂₆₆ alkyl, C₃₆₆ alkoxy, C₄₆₆ alkylthio, C₅₆₆ alkanoyl, C₆₆₆ alkanoyloxy, nitro, C₇₆₆ alkylamino, amino, halogen, trifluoromethyl, C₁₆₆ alkylsulfonyl and C₁₆₆ alkylsulfonyl; m is 1 or 2;
or a pharmaceutically or veterinarily acceptable salt or ester thereof.
2. A compound according to claim 1, wherein R₁ is —OCH(Phenyl)₂, R₂ is methyl, R₃ and R₄ are 2′-phenyl, R₅ is Br and m = 2.
3. A pharmaceutical composition for controlling inflammatory or degenerative conditions in a mammal comprising an effective amount of a compound of claim 1 in admixture with a pharmaceutically acceptable carrier.
4. A method of controlling inflammatory or degenerative conditions in a mammal, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to claim 1.
5. A method of treating an elastase-mediated pathological condition in humans which comprises administering a physiologically acceptable form of the compound of claim 1.
6. A pharmaceutical composition for controlling inflammatory or degenerative conditions in a mammal comprising an effective amount of a compound of claim 2 in admixture with a pharmaceutically acceptable carrier.
7. A method of controlling inflammatory or degenerative conditions in a mammal, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to claim 2.
8. A method of treating an elastase-mediated pathological condition in humans which comprises administering a physiologically acceptable form of the compound of claim 2.

9. A compound according to claim 1 which is selected from the group consisting of:
   benzhydryl 7a-chloro-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7,7-dehydro-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;
   benzhydryl 7a-bromo-2-spiro (2′,2′-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;